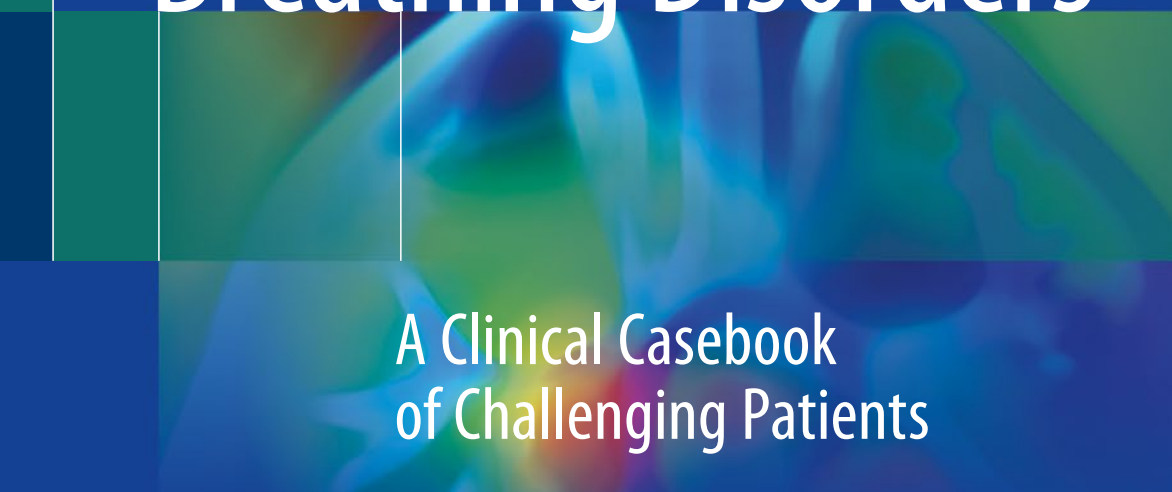
Complex Sleep Breathing Disorders



A Clinical Casebook of Challenging Patients

Christine Won
Editor

Springer

Complex Sleep Breathing Disorders

Christine Won
Editor

Complex Sleep Breathing Disorders

A Clinical Casebook of Challenging Patients

Springer

Editor
Christine Won
Pulmonary, Critical Care and Sleep Medicine
Yale University
New Haven, CT
USA

ISBN 978-3-030-57941-8 ISBN 978-3-030-57942-5 (eBook)
https://doi.org/10.1007/978-3-030-57942-5

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

I dedicate this book to my forever inspirations, Ella and Sofia.

Preface

There was a time when sleep disordered breathing was defined by obstructive sleep apnea, and only obstructive sleep apnea. The field has since evolved tremendously. With advanced diagnostic tools and technology in conjunction with more sophisticated data interpretation, we now recognize that in fact multiple different types of sleep-related breathing disorders exist. Even within the categories of obstructive sleep apnea, central sleep apnea, sleep-related hypoventilation or hypoxemia, there are many disease phenotypes. Even "simple" obstructive sleep apnea is now recognized as a diverse and complex disease process brought about not just from obesity or a crowded anatomy, but also as a result of abnormal ventilatory drive, altered arousal threshold, or exaggerated upper airway collapsibility.

Likewise, there was a time when CPAP was the only treatment for sleep disordered breathing, and the only setting requiring adjustment was the fixed pressure. Now, there is literally an alphabet soup of positive airway pressure modalities, with many nuanced settings and features. We know that patients respond differently to treatment. We also know that certain modes of positive pressure may be harmful in some diseases. This speaks to the essential nature of understanding the disorder one is treating.

This book presents several cases of complex sleep-related breathing disorders along with their treatment challenges and approaches. As the medical director of a large tertiary academic sleep center servicing over 11,000 patients, I have come to appreciate the diversity and complexity of sleep-related breathing disorders. Very few cases are "straightforward OSA," and understanding this offers the best likelihood for treatment success.

New Haven, CT, USA — Christine Won

Contents

Contributors

Loutfi S. Aboussouan, MD Respiratory Institute, Cleveland Clinic, Cleveland, OH, USA

Gabriel Anders, DO, MHA Division of Pulmonary, Sleep and Critical Care Medicine, University of Missouri-Kansas City, Kansas City, MO, USA

M. Safwan Badr, MD, MBA Department of Internal Medicine, Wayne State University School of Medicine, University Health Center, Detroit, MI, USA

Mustafa Bseikri, MD Pediatric Pulmonary & Sleep Medicine, Kaiser Permanente – Northern California, Northern California, CA, USA

Aditya Chada, MD Emory University, Atlanta, GA, USA

Nancy Collop, MD Emory University, Atlanta, GA, USA

Anthony G. Doufas, MD, PhD Stanford University School of Medicine, Stanford, CA, USA

Umur Hatipoğlu, MD Respiratory Institute, Cleveland Clinic, Cleveland, OH, USA

Robert Hiensch, MD Icahn School of Medicine at Mount Sinai, Mount Sinai Hospital, Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, New York, NY, USA

Janet Hilbert, MD Pulmonary, Critical Care and Sleep Medicine, Yale University, New Haven, CT, USA

David G. Ingram, MD Children's Mercy Hospital, Kansas City, MO, USA

S. Javaheri Bethesda North Hospital, Cincinnati, OH, USA

Sunjeet Kaur, MD Case Western Reserve University Metro Health, Cleveland, OH, USA

Ilya Khaytin, MD, PhD Division of Pediatric Autonomic Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago and Stanley Manne Children's Research Institute, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Douglas B. Kirsch, MD Atrium Health, UNC School of Medicine, Charlotte, NC, USA

Jisoo Lee, MD Rhode Island Hospital, Pulmonary, Critical Care Medicine and Sleep, Providence, RI, USA

Javier Lorenzo, MD Stanford University School of Medicine, Stanford, CA, USA

Stephanie M. Marshall, MD Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Division of Neonatology, Ann & Robert H. Lurie Children's Hospital of Chicago and Stanley Manne Children's Research Institute, Chicago, IL, USA

Reena Mehra, MD, MS, FCCP, FAASM Department of Sleep Medicine, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA

K. Nicole Mims, MD, MS Atrium Health, Charlotte, NC, USA

Vahid Mohsenin, MD, FCCP Section of Pulmonary, Critical Care and Sleep Medicine, Yale University, New Haven, CT, USA

Caroline U. A. Okorie, MD, MPH Lucile Packard Children's Hospital, Stanford University School of Medicine, Department of Pediatrics, Division of Pulmonary, Asthma and Sleep, Palo Alto, CA, USA

Jeremy E. Orr, MD Division of Pulmonary, Critical Care, and Sleep Medicine, University of California San Diego, San Diego, CA, USA

Robert L. Owens, MD Division of Pulmonary, Critical Care, and Sleep Medicine, University of California San Diego, San Diego, CA, USA

Melanie Pogach, MD, MMSc Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA

David M. Rapoport Icahn School of Medicine at Mount Sinai, Mount Sinai Hospital, Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, New York, NY, USA

Ashima Sahni Northwestern Memorial, Department of Medicine, Chicago, IL, USA

Anan Salloum, MD Wayne State University, John D. Dingell VA Medical Center, Detroit, MI, USA

Bernardo J. Selim, MD Mayo Clinic Center for Sleep Medicine, Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA

Katherine M. Sharkey, MD, PhD, FAASM The Warren Alpert Medical School of Brown University, Providence, RI, USA

Susan M. Slattery, MD, MS Division of Pediatric Autonomic Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago and Stanley Manne Children's Research Institute, Chicago, IL, USA

Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Division of Neonatology, Ann & Robert H. Lurie Children's Hospital of Chicago and Stanley Manne Children's Research Institute, Chicago, IL, USA

Shannon S. Sullivan, MD Pediatric Pulmonary & Sleep Medicine, Stanford University, Palo Alto, CA, USA

Sritika Thapa, MD Pulmonary, Critical Care and Sleep Medicine, Yale University, New Haven, CT, USA

Robert Thomas, MD, MMSc Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA

J. Verbraecken, MD, PhD Department of Pulmonary Medicine and Multidisciplinary Sleep Disorders Centre, Antwerp University Hospital and University of Antwerp, Antwerp, Belgium

Debra E. Weese-Mayer, MD Division of Neonatology, Ann & Robert H. Lurie Children's Hospital of Chicago and Stanley Manne Children's Research Institute, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Pnina Weiss, MD Department of Pediatrics, Section of Respiratory, Allergy-Immunology and Sleep Medicine, Yale School of Medicine, New Haven, CT, USA

Lisa Wolfe, MD Northwestern Memorial, Department of Medicine, Chicago, IL, USA

Henry Klar Yaggi, MD, MPH Pulmonary, Critical Care and Sleep Medicine, Yale University, New Haven, CT, USA

Faisal Zahiruddin, DO Emory University, Atlanta, GA, USA

Pulmonary, Critical Care, and Sleep Medicine, Houston Methodist Hospital, Houston, TX, USA

Andrey Zinchuk, MD, MHS Pulmonary, Critical Care and Sleep Medicine, Yale University, New Haven, CT, USA

Chapter 1
Hypercapnic Obstructive Sleep Apnea

Melanie Pogach and Robert Thomas

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.

M. Pogach · R. Thomas (✉)
Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA
e-mail: rthomas1@bidmc.harvard.edu

C. Won (ed.), *Complex Sleep Breathing Disorders*,
https://doi.org/10.1007/978-3-030-57942-5_1

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

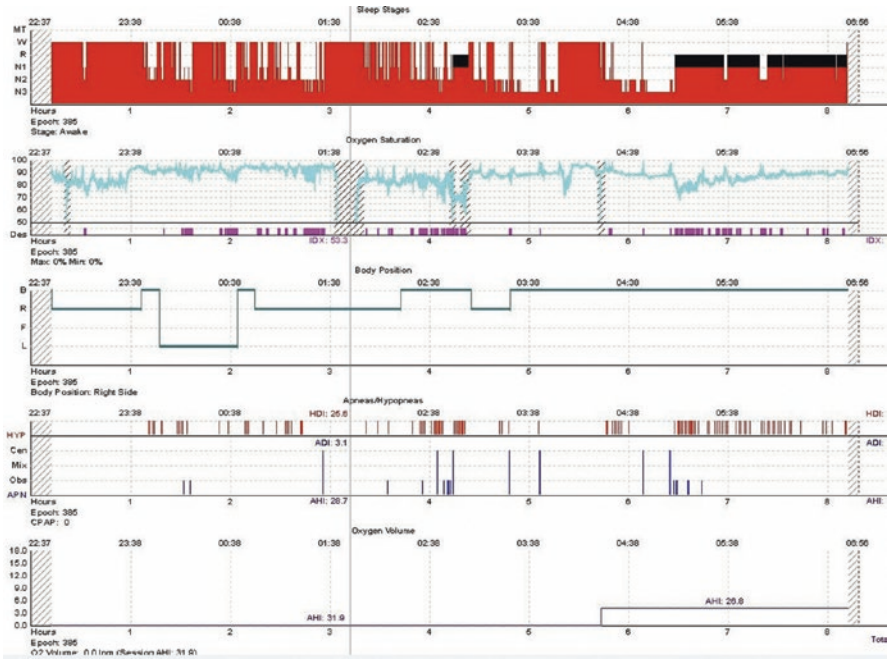


Fig. 1.1 Hypercapnic obstructive sleep apnea hypnogram. Notable abnormalities are severe sleep fragmentation and sustained hypoxia even when respiratory events are scarce. Though not in this figure, there was hypercapnia (see Fig. 1.2) associated with the hypoxia

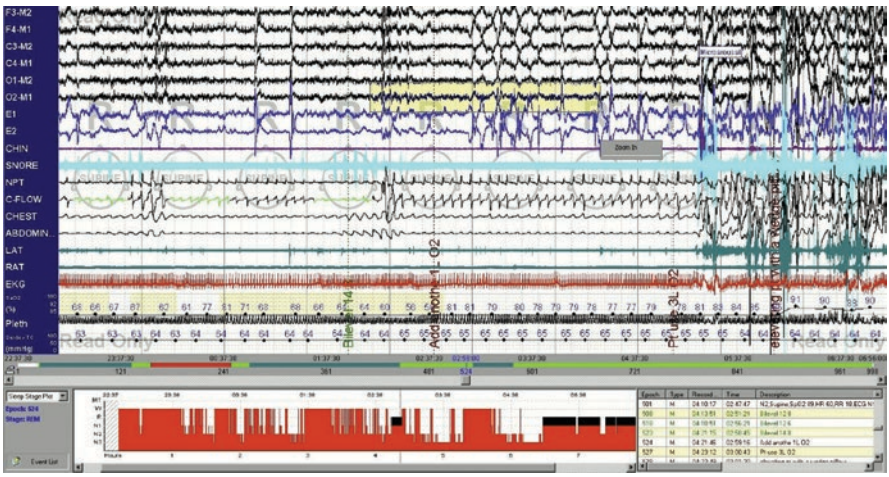


Fig. 1.2 Severe hypercapnia and hypoxia during positive pressure (bilevel) titration. The same patient as in Fig. 1.1. Though sleep is starting to show improved consolidation, there is severe hypoxia and substantial hypercapnia; this snapshot is from rapid eye movement sleep

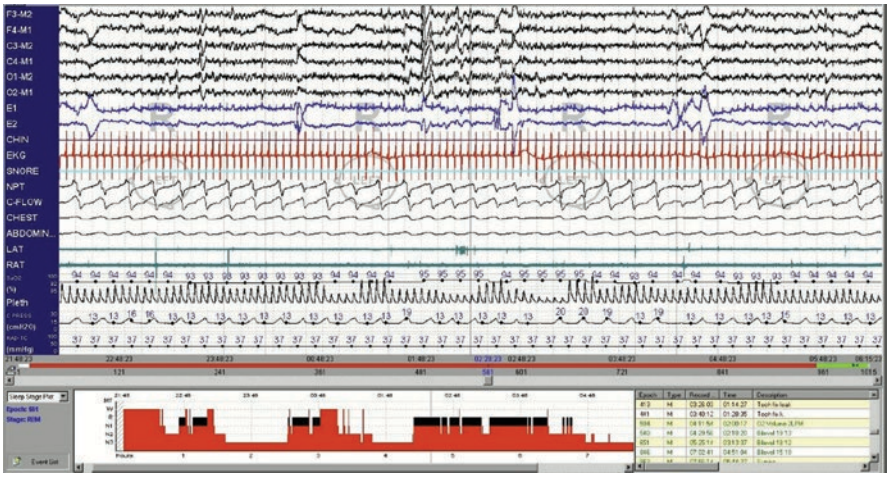


Fig. 1.3 Effect of positive airway pressure treatment on hypercapnic obstructive sleep apnea. Same patient as in Figs. 1.1 and 1.2, a repeat titration after 1 month of bilevel ventilation. Note the marked improvement of sleep consolidation, the persistence of slow wave sleep, and REM rebound and normalization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

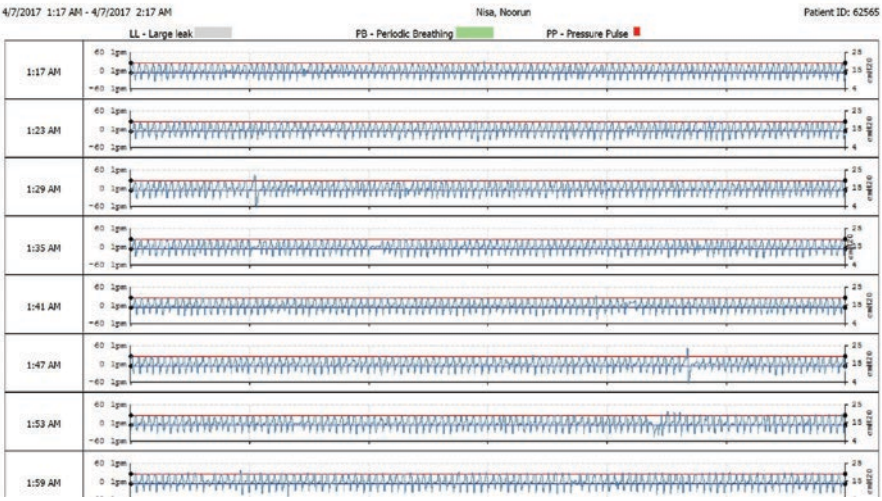


Fig. 1.4 Stable breathing on long-term bilevel ventilation. The same patient as in Figs. 1.1, 1.2, and 1.3. Stable breathing documented through the online EncoreAnywhere™ system. Each horizontal line is 6 min. Inspiratory pressure is the horizontal red line, expiratory pressure the horizontal blue line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

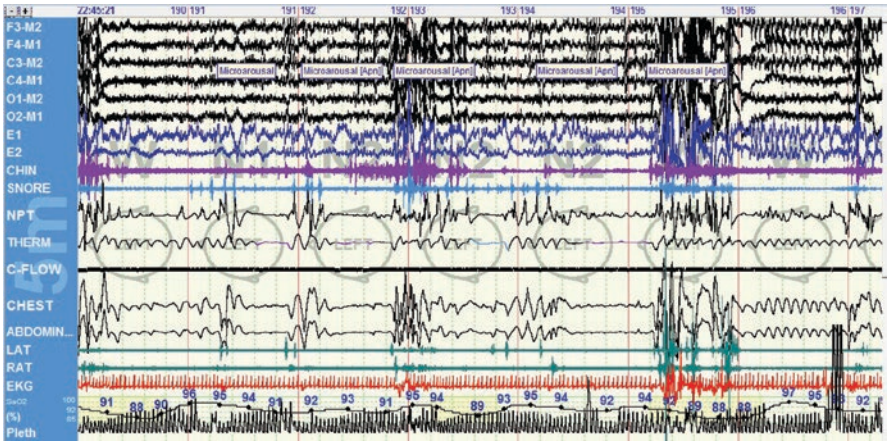


Fig. 1.5 Polysomnographic phenotype of high loop gain obstructive sleep apnea. Note the short cycle lengths (less than 30 s) and the free admixture of obstructive and central events, in non-rapid eye movement sleep

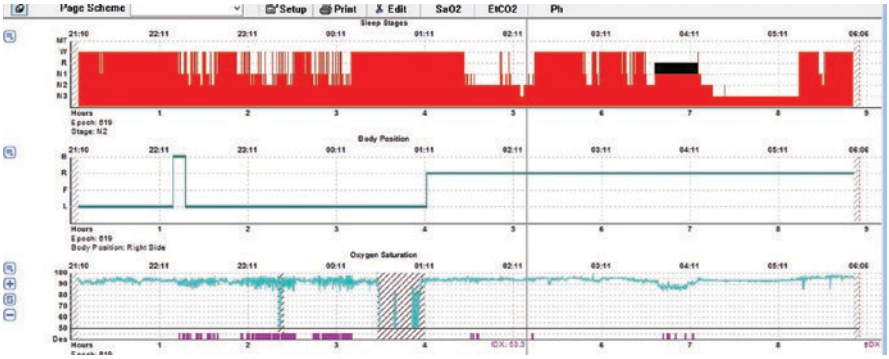


Fig. 1.6 Hypnogram of AVAPS followed by CPAP titration. High loop gain signal in a hypercarbic patient. The same patient as in Fig. 1.5 and this figure. The clue to a high loop gain is the pattern of oxygen desaturations – a "band-like" pattern, which occurs only in the presence of high loop gain and 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.

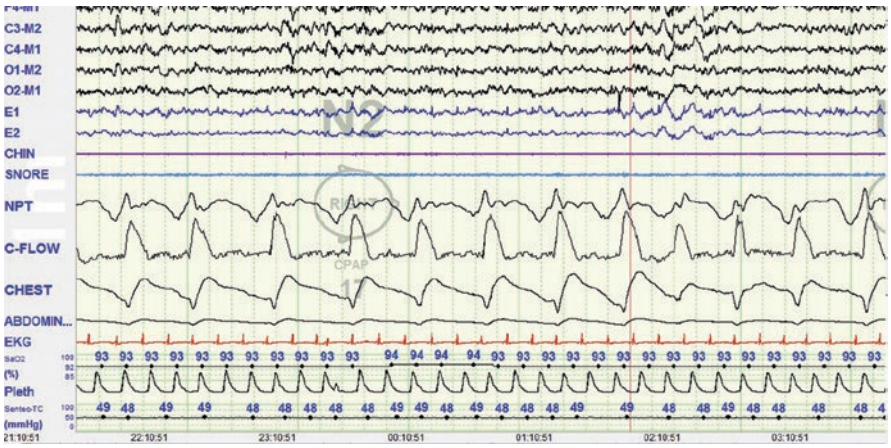


Fig. 1.7 Treatment of high loop gain hypercapnic OSA. CPAP, non-vented mask to buffer CO_2 fluctuations, and 2 L/min supplemental oxygen added to CPAP. This mask configuration reduces CO_2 fluctuations and thus aids in stabilization of respiratory motor output. Though stabilized, the patient is mildly 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.

References

1. Longobardo GS, Evangelisti CJ, Cherniack NS. Analysis of the interplay between neurochemical control of respiration and upper airway mechanics producing upper airway obstruction during sleep in humans. Exp Physiol. 2008;93(2):271–87.
2. Mokhlesi B. Obesity hypoventilation syndrome: a state-of-the-art review. Respir Care. 2010;55(10):1347–62; discussion 1363–1345.
3. Weese-Mayer DE, Berry-Kravis EM, Ceccherini I, Keens TG, Loghmanee DA, Trang H. An official ATS clinical policy statement: congenital central hypoventilation syndrome: genetic basis, diagnosis, and management. Am J Respir Crit Care Med. 2010;181(6):626–44.
4. Iturriaga R, Moya EA, Del Rio R. Carotid body potentiation induced by intermittent hypoxia: implications for cardiorespiratory changes induced by sleep apnoea. Clin Exp Pharmacol Physiol. 2009;36(12):1197–204.
5. Richalet JP, Larmignat P, Poitrine E, Letournel M, Canoui-Poitrine F. Physiological risk factors for severe high-altitude illness: a prospective cohort study. Am J Respir Crit Care Med. 2012;185(2):192–8.
6. Giannoni A, Emdin M, Bramanti F, et al. Combined increased chemosensitivity to hypoxia and hypercapnia as a prognosticator in heart failure. J Am Coll Cardiol. 2009;53(21):1975–80.

7. Giannoni A, Emdin M, Poletti R, et al. Clinical significance of chemosensitivity in chronic heart failure: influence on neurohormonal derangement, Cheyne-stokes respiration and arrhythmias. Clin Sci (Lond). 2008;114(7):489–97.
8. Gilmartin GS, Lynch M, Tamisier R, Weiss JW. Chronic intermittent hypoxia in humans during 28 nights results in blood pressure elevation and increased muscle sympathetic nerve activity. Am J Physiol Heart Circ Physiol. 2010;299(3):H925–31.
9. Gilmartin GS, Tamisier R, Curley M, Weiss JW. Ventilatory, hemodynamic, sympathetic nervous system, and vascular reactivity changes after recurrent nocturnal sustained hypoxia in humans. Am J Physiol Heart Circ Physiol. 2008;295(2):H778–85.
10. Tamisier R, Hunt BE, Gilmartin GS, Curley M, Anand A, Weiss JW. Hemodynamics and muscle sympathetic nerve activity after 8 h of sustained hypoxia in healthy humans. Am J Physiol Heart Circ Physiol. 2007;293(5):H3027–35.
11. Strohl KP. Periodic breathing and genetics. Respir Physiol Neurobiol. 2003;135(2–3):179–85.
12. Tankersley CG, Fitzgerald RS, Kleeberger SR. Differential control of ventilation among inbred strains of mice. Am J Phys. 1994;267(5 Pt 2):R1371–7.
13. Oyamada Y, Yamaguchi K, Murai M, Hakuno H, Ishizaka A. Role of Kir2.2 in hypercapnic ventilatory response during postnatal development of mouse. Respir Physiol Neurobiol. 2005;145(2–3):143–51.
14. Lahiri S, Maret K, Sherpa MG. Dependence of high altitude sleep apnea on ventilatory sensitivity to hypoxia. Respir Physiol. 1983;52(3):281–301.
15. Dunai J, Kleiman J, Trinder J. Ventilatory instability during sleep onset in individuals with high peripheral chemosensitivity. J Appl Physiol. 1999;87(2):661–72.
16. Ponikowski P, Banasiak W. Chemosensitivity in chronic heart failure. Heart Fail Monit. 2001;1(4):126–31.
17. Nopmaneejumruslers C, Kaneko Y, Hajek V, Zivanovic V, Bradley TD. Cheyne-Stokes respiration in stroke: relationship to hypocapnia and occult cardiac dysfunction. Am J Respir Crit Care Med. 2005;171(9):1048–52.
18. Mansfield DR, Solin P, Roebuck T, Bergin P, Kaye DM, Naughton MT. The effect of successful heart transplant treatment of heart failure on central sleep apnea. Chest. 2003;124(5):1675–81.
19. McGinty D, Littner M, Beahm E, Ruiz-Primo E, Young E, Sowers J. Sleep related breathing disorders in older men: a search for underlying mechanisms. Neurobiol Aging. 1982;3(4):337–50.
20. 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(1):14–20.
21. Fletcher EC. Recurrence of sleep apnea syndrome following tracheostomy. A shift from obstructive to central apnea. Chest. 1989;96(1):205–9.
22. Chenuel BJ, Smith CA, Skatrud JB, Henderson KS, Dempsey JA. Increased propensity for apnea in response to acute elevations in left atrial pressure during sleep in the dog. J Appl Physiol. 2006;101(1):76–83.
23. Dursunoglu N, Dursunoglu D, Ozkurt S, Gur S, Ozalp G, Evyapan F. Effects of CPAP on right ventricular myocardial performance index in obstructive sleep apnea patients without hypertension. Respir Res. 2006;7(1):22.
24. Shivalkar B, Van de Heyning C, Kerremans M, et al. Obstructive sleep apnea syndrome: more insights on structural and functional cardiac alterations, and the effects of treatment with continuous positive airway pressure. J Am Coll Cardiol. 2006;47(7):1433–9.
25. Niroumand M, Kuperstein R, Sasson Z, Hanly PJ. Impact of obstructive sleep apnea on left ventricular mass and diastolic function. Am J Respir Crit Care Med. 2001;163(7):1632–6.
26. Mahamed S, Hanly PJ, Gabor J, Beecroft J, Duffin J. Overnight changes of chemoreflex control in obstructive sleep apnoea patients. Respir Physiol Neurobiol. 2005;146(2–3):279–90.
27. Spicuzza L, Bernardi L, Balsamo R, Ciancio N, Polosa R, Di Maria G. Effect of treatment with nasal continuous positive airway pressure on ventilatory response to hypoxia and hypercapnia in patients with sleep apnea syndrome. Chest. 2006;130(3):774–9.

28. Salloum A, Rowley JA, Mateika JH, Chowdhuri S, Omran Q, Badr MS. Increased propensity for central apnea in patients with obstructive sleep apnea: effect of nasal continuous positive airway pressure. Am J Respir Crit Care Med. 2010;181(2):189–93.
29. Dempsey JA, Smith CA, Przybylowski T, et al. The ventilatory responsiveness to CO(2) below eupnoea as a determinant of ventilatory stability in sleep. J Physiol. 2004;560(Pt 1):1–11.
30. Nakayama H, Smith CA, Rodman JR, Skatrud JB, Dempsey JA. Carotid body denervation eliminates apnea in response to transient hypocapnia. J Appl Physiol. 2003;94(1):155–64.
31. Smith CA, Chenuel BJ, Henderson KS, Dempsey JA. The apneic threshold during non-REM sleep in dogs: sensitivity of carotid body vs. central chemoreceptors. J Appl Physiol. 2007;103(2):578–86.
32. Xie A, Skatrud JB, Puleo DS, Dempsey JA. Influence of arterial O_2 on the susceptibility to posthyperventilation apnea during sleep. J Appl Physiol. 2006;100(1):171–7.
33. Szollosi I, Jones M, Morrell MJ, Helfet K, Coats AJ, Simonds AK. Effect of CO_2 inhalation on central sleep apnea and arousals from sleep. Respiration. 2004;71(5):493–8.
34. Khayat RN, Xie A, Patel AK, Kaminski A, Skatrud JB. Cardiorespiratory effects of added dead space in patients with heart failure and central sleep apnea. Chest. 2003;123(5):1551–60.
35. Xie A, Teodorescu M, Pegelow DF, et al. Effects of stabilizing or increasing respiratory motor outputs on obstructive sleep apnea. J Appl Physiol (1985). 2013;115(1):22–33.
36. Gilmartin G, McGeehan B, Vigneault K, et al. Treatment of positive airway pressure treatment-associated respiratory instability with enhanced expiratory rebreathing space (EERS). J Clin Sleep Med. 2010;6(6):529–38.
37. Giannoni A, Baruah R, Willson K, et al. Real-time dynamic carbon dioxide administration: a novel treatment strategy for stabilization of periodic breathing with potential application to central sleep apnea. J Am Coll Cardiol. 2010;56(22):1832–7.
38. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. J Clin Sleep Med. 2012;8(5):597–619.
39. Jobin V, Rigau J, Beauregard J, et al. Evaluation of upper airway patency during cheyne-stokes breathing in heart failure patients. Eur Respir J. 2012;40:1523–30.
40. Thomas RJ, Tamisier R, Boucher J, et al. Nocturnal hypoxia exposure with simulated altitude for 14 days does not significantly alter working memory or vigilance in humans. Sleep. 2007;30(9):1195–203.
41. Badr MS, Toiber F, Skatrud JB, Dempsey J. Pharyngeal narrowing/occlusion during central sleep apnea. J Appl Physiol. 1995;78(5):1806–15.
42. Sankri-Tarbichi AG, Rowley JA, Badr MS. Expiratory pharyngeal narrowing during central hypocapnic hypopnea. Am J Respir Crit Care Med. 2009;179(4):313–9.
43. Westhoff M, Arzt M, Litterst P. Prevalence and treatment of central sleep apnoea emerging after initiation of continuous positive airway pressure in patients with obstructive sleep apnoea without evidence of heart failure. Sleep Breath. 2012;16(1):71–8.
44. Javaheri S, Smith J, Chung E. The prevalence and natural history of complex sleep apnea. J Clin Sleep Med. 2009;5(3):205–11.
45. Thomas RJ, Terzano MG, Parrino L, Weiss JW. Obstructive sleep-disordered breathing with a dominant cyclic alternating pattern--a recognizable polysomnographic variant with practical clinical implications. Sleep. 2004;27(2):229–34.
46. Thomas RJ, Mietus JE, Peng CK, et al. Differentiating obstructive from central and complex sleep apnea using an automated electrocardiogram-based method. Sleep. 2007;30(12):1756–69.
47. Shore ET, Millman RP. Central sleep apnea and acetazolamide therapy. Arch Intern Med. 1983;143(6):1278, 1280.
48. Inoue Y, Takata K, Sakamoto I, Hazama H, Kawahara R. Clinical efficacy and indication of acetazolamide treatment on sleep apnea syndrome. Psychiatry Clin Neurosci. 1999;53(2):321–2.
49. Edwards BA, Sands SA, Eckert DJ, et al. Acetazolamide improves loop gain but not the other physiological traits causing obstructive sleep apnoea. J Physiol. 2012;590(Pt 5):1199–211.
50. Edwards BA, Connolly JG, Campana LM, et al. Acetazolamide attenuates the ventilatory response to arousal in patients with obstructive sleep apnea. Sleep. 2013;36(2):281–5.

51. Teppema LJ. Multifaceted clinical effects of acetazolamide: will the underlying mechanisms please stand up? J Appl Physiol (1985). 2014;116(7):713–4.
52. Nakayama H, Smith CA, Rodman JR, Skatrud JB, Dempsey JA. Effect of ventilatory drive on carbon dioxide sensitivity below eupnea during sleep. Am J Respir Crit Care Med. 2002;165(9):1251–60.
53. Javaheri S. Acetazolamide improves central sleep apnea in heart failure: a double-blind, prospective study. Am J Respir Crit Care Med. 2006;173(2):234–7.
54. Latshang TD, Nussbaumer-Ochsner Y, Henn RM, et al. Effect of acetazolamide and autoCPAP therapy on breathing disturbances among patients with obstructive sleep apnea syndrome who travel to altitude: a randomized controlled trial. JAMA. 2012;308(22):2390–8.
55. Glidewell RN, Orr WC, Imes N. Acetazolamide as an adjunct to CPAP treatment: a case of complex sleep apnea in a patient on long-acting opioid therapy. J Clin Sleep Med. 2009;5(1):63–4.
56. De Simone G, Di Fiore A, Menchise V, et al. Carbonic anhydrase inhibitors. Zonisamide is an effective inhibitor of the cytosolic isozyme II and mitochondrial isozyme V: solution and X-ray crystallographic studies. Bioorg Med Chem Lett. 2005;15(9):2315–20.
57. Westwood AJ, Vendrame M, Montouris G, Auerbach SH. Pearls & Oy-sters: treatment of central sleep apnea with topiramate. Neurology. 2012;78(16):e97–9.
58. Teppema LJ, Swenson ER. The noncarbonic anhydrase inhibiting acetazolamide analog N-methylacetazolamide reduces the hypercapnic, but not hypoxic, ventilatory response. Physiol Rep. 2015;3(8):e12484.
59. Eskandari D, Zou D, Grote L, Hoff E, Hedner J. Acetazolamide reduces blood pressure and sleep-disordered breathing in patients with hypertension and obstructive sleep apnea: a randomized controlled trial. J Clin Sleep Med. 2018;14(3):309–17.
60. Norman D, Loredo JS, Nelesen RA, et al. Effects of continuous positive airway pressure versus supplemental oxygen on 24-hour ambulatory blood pressure. Hypertension. 2006;47(5):840–5.
61. Gottlieb DJ, Punjabi NM, Mehra R, et al. CPAP versus oxygen in obstructive sleep apnea. N Engl J Med. 2014;370(24):2276–85.
62. Edwards BA, Sands SA, Owens RL, et al. Effects of hyperoxia and hypoxia on the physiological traits responsible for obstructive sleep apnoea. J Physiol. 2014;592(Pt 20):4523–35.
63. Wellman A, Malhotra A, Jordan AS, Stevenson KE, Gautam S, White DP. Effect of oxygen in obstructive sleep apnea: role of loop gain. Respir Physiol Neurobiol. 2008;162(2):144–51.
64. Allam JS, Olson EJ, Gay PC, Morgenthaler TI. Efficacy of adaptive servoventilation in treatment of complex and central sleep apnea syndromes. Chest. 2007;132(6):1839–46.
65. Edwards BA, Sands SA, Owens RL, et al. Effects of hyperoxia and hypoxia on the physiological traits responsible for obstructive sleep apnoea. J Physiol. 2014;592:4523–35.
66. Chowdhuri S, Ghabsha A, Sinha P, Kadri M, Narula S, Badr MS. Treatment of central sleep apnea in U.S. veterans. J Clin Sleep Med. 2012;8(5):555–63.
67. Gold AR, Bleecker ER, Smith PL. A shift from central and mixed sleep apnea to obstructive sleep apnea resulting from low-flow oxygen. Am Rev Respir Dis. 1985;132(2):220–3.
68. Arzt M, Wensel R, Montalvan S, et al. Effects of dynamic bilevel positive airway pressure support on central sleep apnea in men with heart failure. Chest. 2008;134(1):61–6.
69. Thomas RJ. The chemoreflex and sleep-disordered breathing: man and machine vs. the beast. Sleep Med. 2011;12(6):533–5.
70. Thomas RJ. Positive pressure therapy induced harm - non-linear, adaptive and maladaptive responses. Sleep Med. 2015;12:1582–3.
71. Zhu K, Kharboutly H, Ma J, Bouzit M, Escourrou P. Bench test evaluation of adaptive servoventilation devices for sleep apnea treatment. J Clin Sleep Med. 2013;9(9):861–71.
72. Gunn S, Naik S, Bianchi MT, Thomas RJ. Estimation of adaptive ventilation success and failure using polysomnogram and outpatient therapy biomarkers. Sleep. 2018;41:zsy033.
73. Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. N Engl J Med. 2015;373(12):1095–105.
74. Ayas NT, Patil SP, Stanchina M, Malhotra A. Treatment of central sleep apnea with adaptive Servoventilation in chronic heart failure. Am J Respir Crit Care Med. 2015;192:132–3.

Chapter 2
Central Sleep Apnea and Opioid Use

Jeremy E. Orr and Robert L. Owens

Case

A 65-year-old man was admitted to the hospital following an endoscopy with suspected aspiration pneumonia. He was obese (BMI 33 kg/m^2) and had been diagnosed with obstructive sleep apnea (OSA). He had used continuous positive airway pressure (CPAP) in the past but stopped 2 years ago. He also had a history of chronic pancreatitis, Whipple surgery, and chronic pain managed with an intrathecal pain pump and oral opioids. In the hospital he was found to have decompensated hypercapnia and hypoxemia requiring admission to the intensive care unit. Subsequently he was transitioned to the medical ward, where continuous supplemental oxygen was continued, and he was started on nocturnal bilevel positive airway pressure (bilevel-S), with an inspiratory positive airway pressure (IPAP) of 10 and expiratory positive airway pressure (EPAP) of 5.

After discharge, the patient was subsequently referred to sleep clinic. On evaluation, he endorsed sleep fragmentation and daytime sleepiness and had not felt any improvement with bilevel, with use averaging >5 h per night. His medications included baclofen 10 mg PO TID, sertraline 100 mg PO daily, doxazosin 8 mg PO daily, morphine 30 mg PO q6hrs as needed for pain (using 2–3 times per day), intrathecal dilaudid at 9 mg per day, testosterone gel 5 grams topical daily, and pancrelipase with meals. A polysomnogram with bilevel titration was ordered and revealed central sleep apnea (CSA). Results of the study are shown in Fig. 2.1. Given the failure to control his sleep-disordered breathing and in the absence of any contraindication (i.e., decreased ejection fraction), the patient then underwent titration with adaptive servo-ventilation (ASV), the results of which are shown in Fig. 2.2.

J. E. Orr (✉) · R. L. Owens
Division of Pulmonary, Critical Care, and Sleep Medicine, University of California San Diego, San Diego, CA, USA
e-mail: j1orr@ucsd.edu

C. Won (ed.), *Complex Sleep Breathing Disorders*,
https://doi.org/10.1007/978-3-030-57942-5_2

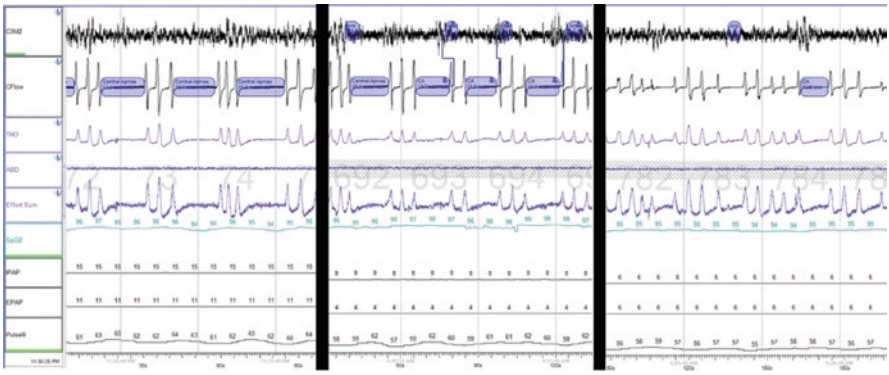


Fig. 2.1 Titration study. Panel (1) – patient while using bilevel-S, with settings of IPAP 15, EPAP 11. Note regularly irregular breathing pattern with persistence of central apneas. Panel (2) – bilevel-S pressures were later down titrated to IPAP 8 and EPAP 4, with persistence of central apneas and more irregularity. Panel (3) – patient switched to CPAP, set at 6. Note improvement in central apneas but increased irregularity of respiratory rate and tidal volume (i.e., "ataxic" pattern). *C3M2* electroencephalogram, *C Flow* volumetric flow, *THO* thoracic excursion, *ABD* abdominal excursion, SpO_2 oxyhemoglobin saturation (%), *IPAP* inspiratory positive airway pressure, *EPAP* expiratory positive airway pressure

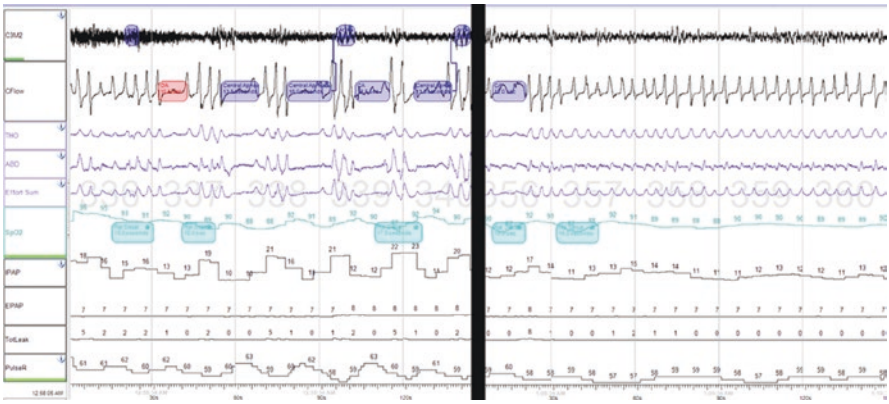


Fig. 2.2 Repeat titration study. Panel (1) – patient using adaptive servo-ventilation, with persistence of unstable breathing and central apneas. Note large fluctuations of IPAP, with highest IPAP levels coinciding with hyperpneic phase, potentially perpetuating instability. Panel (2) – patient remains on adaptive servo-ventilation, with eventual stabilization of breathing. Note minimal IPAP pressure changes once breathing has stabilized. *C3M2* electroencephalogram, *C Flow* volumetric flow, *THO* thoracic excursion, *ABD* abdominal excursion, SpO_2 oxyhemoglobin saturation (%), *IPAP* inspiratory positive airway pressure, *EPAP* expiratory positive airway pressure

He was subsequently started on ASV at home. At 3-month follow-up, he noted greatly decreased awakenings from sleep and substantially improved energy during the day, although his sleep remained disrupted by pain, and he was taking naps on most days. Given his ongoing supplemental oxygen use, nocturnal oximetry was performed, with saturation <89% for 1 h and 51 min. He was weaned off daytime oxygen and maintained on 2 L/min via his ASV device at night. Pulmonary workup was notable for mild restrictive lung disease attributed to left hemidiaphragm elevation. Over the ensuing several months, his sleep continued to improve, and compliance continued to rise, currently averaging >6 h per night. He was followed by his pain specialist and weaned down on his intrathecal dilaudid to 5 mg daily and using morphine less frequently.

Discussion

Introduction

Chronic opioid use has increased over the past several decades, measured by a number of different metrics [1, 2]. There are likely multiple factors that have driven this increase, including extrapolation of safety and efficacy from small studies and an influential report that suggested that pain was undertreated and opioids underutilized [3, 4]. Unfortunately, this increase in opioid prescriptions has come with substantial downsides. There has been a concurrent increase in illicit opioid use and dependence, likely fueled in part by wide availability of diverted prescription opioids, and the legitimate use of opioids which may play a role in the pathway toward abuse among certain individuals. Respiratory complications have been prominent; opioid-induced respiratory depression contributed to over 42,000 drug-related deaths in 2016 [5]. Although many of these deaths are due to illicit abuse, those using opioids even as prescribed may also be affected. Beyond the fatal or nearly fatal respiratory depression events that may occur in patients using opioids, evidence has also shown that the respiratory effects of chronic opioid use may lead to the development of opioid-induced central sleep apnea (O-CSA), a condition which presents a number of challenges for clinicians.

There are major efforts underway to decrease the use of opioids for the management of chronic pain and to counteract abuse of opioids. However, for those with prior opioid abuse or pain-related indications, a substantial proportion of individuals are managed with chronic opioid maintenance (including methadone, Suboxone, and intrathecal opioids), rather than complete cessation. As such, although O-CSA improves with dose reduction or abstinence, it is likely that chronic opioid use with resulting central sleep apnea will continue to be encountered commonly in clinical practice.

Diagnosis

Central sleep apnea due to opioids is classified by the International Classification of Sleep Disorders, third edition, as a form of "Central sleep apnea due to a medication or substance" [6]. The diagnostic criteria are listed below:

1. Polysomnography demonstrates five or more central apneas or hypopneas per hour of sleep.
2. The number of central apneas or hypopneas is greater than 50% of the total number of apneas and hypopneas.
3. The presence of signs or symptoms, including sleepiness, insomnia (difficulty initiating or maintaining sleep, frequent awakenings, or non-restorative sleep), awakening with shortness of breath, snoring, or witnessed apneas.
4. The patient is taking an opioid medication.

Beyond these diagnostic criteria, O-CSA can often be recognized by a characteristic breathing pattern, which is erratic in nature and is classically described as "ataxic" (case example – Fig. 2.1). This pattern was originally described in 1876 as Biot's respirations, a pattern encountered in those with severe brain injury. Changes in ventilation are abrupt, lacking the crescendo-decrescendo pattern seen in Cheyne-Stokes respirations. In practice, the regularity of breathing can be variable; some patients demonstrate highly irregular respiratory rates, while others are more "regularly irregular," in some ways similar to consistent cardiac arrhythmias (e.g., 3:2 atrial flutter). While the duration of apneas/hypopneas and ventilation/hyperpneas is variable, the average overall cycling time (i.e., mean duration of each apnea/hypopnea plus subsequent ventilation/hyperpnea) is not prolonged, generally in a similar 30–40-second range seen in idiopathic CSA. The overall mean respiratory rate may be low, and blood gas abnormalities (in both sleep and wake) such as hypercapnia and sustained hypoxemia can be seen [7–9] (Fig. 2.3).

There are a few caveats regarding the diagnostic testing of O-CSA. Although the American Academy of Sleep Medicine (AASM) provides criteria for the scoring of hypopneas, in practice there can be substantial uncertainty in identification. With severely ataxic breathing and frequent arousals, a baseline level of ventilation by which to compare suspected events can be difficult. In addition, differentiating central from obstructive hypopneas relies on indirect measures of upper airway obstruction such as snoring, flow limitation, and respiratory effort dynamics. Gold-standard techniques for measuring central versus obstructive events rely on esophageal or epiglottic pressure measurement throughout sleep, which is not practical in the clinical setting. As such, categorizing hypopneas as central versus obstructive is considered optional by the AASM, and in our experience, many sleep laboratories simply report "hypopneas," which are not included in the central events index. Effectively, this may lead to an underdiagnosis of CSA, as substantial central apneas would need to be present in order to meet diagnostic criteria. Metrics to quantify ataxic breathing have been reported in research but are not validated for clinical diagnostic

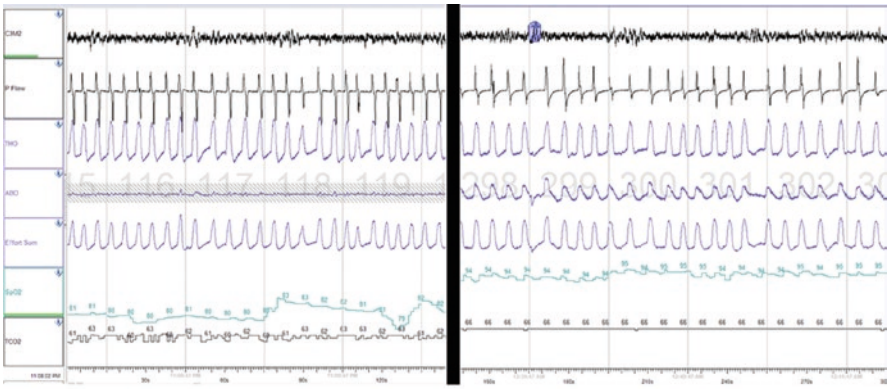


Fig. 2.3 Diagnostic polysomnography in a 77-year-old woman with chronic opioid use (oral oxycodone 5 mg every 6 hours as needed and intrathecal morphine pump). Shown during NREM sleep. (Left panel) The patient has very low baseline saturation with occasional desaturation and severe baseline hypercapnia. Note the bradypnea and irregularity of rate and tidal volume but absence of respiratory events meeting AASM criteria. (Right panel) After starting supplemental oxygen at 1 L/min. 5-min window from NREM sleep. Note improvement in saturation but slight worsening of bradypnea and hypercapnia. Also, respiratory irregularity persists. *C3M2* electroencephalogram, *P Flow* nasal pressure, *THO* thoracic excursion, *ABD* abdominal excursion, SpO_2 oxyhemoglobin saturation (%), TCO_2 transcutaneous carbon dioxide tension (mm Hg)

use. In our case example (Fig. 2.1, right panel), ataxic breathing is noted throughout the window; the presence of one central apnea does not capture the severe breathing abnormalities.

A separate point is that current diagnostic criteria require the use of in-laboratory polysomnography. Based on factors such as advances in technology, increases in patient numbers, and changes to reimbursement, the use of home sleep apnea testing (HSAT) has greatly increased over the past decade. AASM recommends HSAT only for suspected obstructive sleep apnea. Prior studies in patients with heart failure suggest variable performance of HSAT for the diagnosis of CSA [10, 11]. Potential issues with HSAT in this population include aforementioned challenges with scoring hypopneas with ataxic breathing, pain-related sleep disruption that will tend to lead to underestimates of severity, and more universal issues such as improper device application. In the absence of data specifically examining the diagnostic performance for O-CSA and a potential lack of coverage for subsequent treatment, HSAT is not currently recommended. However, it is common in clinical practice to encounter patterns suspicious for O-CSA given the proliferation of HSAT (Fig. 2.4). In our case, HSAT may have enabled earlier consideration for O-CSA during his initial inpatient hospital stay.

In patients with a breathing pattern consistent with O-CSA, with an appropriate opioid use history, and without other clinical indications, we do not recommend other testing (e.g., MRI of the brain) to evaluate for other causes of CSA.

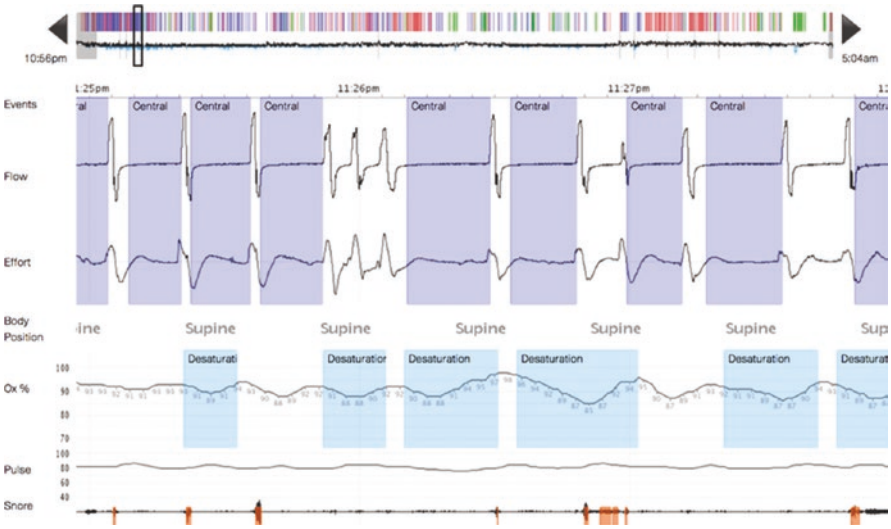


Fig. 2.4 Home sleep apnea testing on a hospitalized patient who was observed by nursing to have pauses in breathing and desaturation. Use of portable sleep apnea testing device may have some use as a screening tool for O-CSA

Epidemiology and Risk Factors

The prevalence of central sleep apnea of all types is poorly described, but among those receiving chronic opioids, it has been reported to be variable but generally high [8, 12]. In a US veterans population, the most common cause of CSA was O-CSA – even more common than Cheyne-Stokes respiration pattern seen in congestive heart failure. Some retrospective studies have attempted to quantify the effect of opioids on the central apnea index and observed a modest effect [13], but these studies are from clinic referral populations and thus unlikely to reflect the true CSA prevalence in opioid patients.

Beyond the general association with chronic opioid use, there are a number of factors that appear to determine whether an individual will develop CSA. At present, there are no guidelines that recommend screening specific populations of opioid users for the presence of O-CSA.

Dose The strong dose dependency of CSA has been clearly illustrated in several studies. A retrospective study comparing a cohort of patients using chronic opioids with patients on non-opioid medications demonstrated a significant increase in central apnea index for each 100 mg daily morphine equivalent increase [14]. Almost all patients taking 200 mg morphine equivalents or above had ataxic breathing, versus about half in those using lower doses. Nonetheless, there has been an inconsistent relationship between plasma levels of opioid and presence or severity of CSA, suggesting additional factors play a role.

Opioid Agent The prevalence of CSA may differ among patients receiving different opioid agents, which is likely to be due to structural differences with associated specific pharmacokinetic and pharmacodynamics properties. Methadone has been most consistently implicated in the development of CSA [15]. However, studies of other opioids may be underpowered, and a high prevalence of O-CSA has been reported in patients using other opioids such as buprenorphine/naloxone [8]. Although data is confined to clinical experience, patients using intrathecal opioids – such as in our case example – can also develop O-CSA.

Concurrent Medications Commonly co-administered medications may include benzodiazepines, non-benzodiazepine sedative-hypnotics, trazodone, and other psychoactive medications. These medications are known to have potential effects on sleep-disordered breathing pathogenesis, including respiratory drive and propensity to arousal from sleep [16]. Benzodiazepines have been shown to contribute to CSA among those taking opioids, although it is unclear whether the effect is additive or interactive [15]. As such, a comprehensive review of other medications used by patients is important. In our patient, concomitant use of baclofen may be a contributing factor.

Possible Other Factors Surprisingly, there have been little data comparing the effect of biological sex on the development of CSA due to opioids. Women demonstrate lower chemoreflex sensitivity than men, which translates to a lower risk of other CSA etiologies, including high altitude CSA [17] and Cheyne-Stokes respirations [18]. Given similarities with the pathogenesis of O-CSA, one might speculate a lower risk in women than men. It is likely that genetic variability in components of the opioid metabolism or respiratory control system plays a role in the development of O-CSA among certain individuals [19].

Pathogenesis

The most prominent effect of opioids relates to the effect on respiratory rhythm generation, consistent with the abnormal pattern of breathing observed in CSA due to opioids. Animal models have convincingly shown that collections of neurons within the ventrolateral medulla (termed the pre-Bötzinger complex) are responsible for inspiratory rhythm generation. These pre-Bötzinger neurons express mu-opioid receptors, activation of which attenuates their action potentials to sub-threshold levels [20]. On the other hand, expiratory neurons within the retrotrapezoid nucleus appear to be unaffected; these integrated effects lead to the observed irregular but chronically stable breathing. From the standpoint of overall ventilatory control, chronic opioid use appears to be associated with a reduction in the hypercapnic ventilatory response and increase in the hypoxic ventilatory response [21]. The net effects contribute to overall control system instability, as well as commonly observed hypercapnia and hypoxemia (which themselves can further

promote instability) [9]. A schematic of the potential effect of opioids on respiratory control is shown in Fig. 2.5.

Opioids may have an effect on upper airway dilator muscle activity, although the clinical impact appears to be minimal. In vivo and in vitro models have shown opioids to suppress output from the hypoglossal nucleus [22, 23]. Although upper airway collapse has been observed during acute opioid administration [24], both cross-sectional studies and opioid withdrawal studies have consistently shown little effect on severity of OSA or obstructive respiratory events [12, 13, 25]. Although the reasons are unclear, activation of upper airway dilator muscles by hypercapnia and hypoxemia commonly observed in these patients may offset any central hypoglossal depression [26].

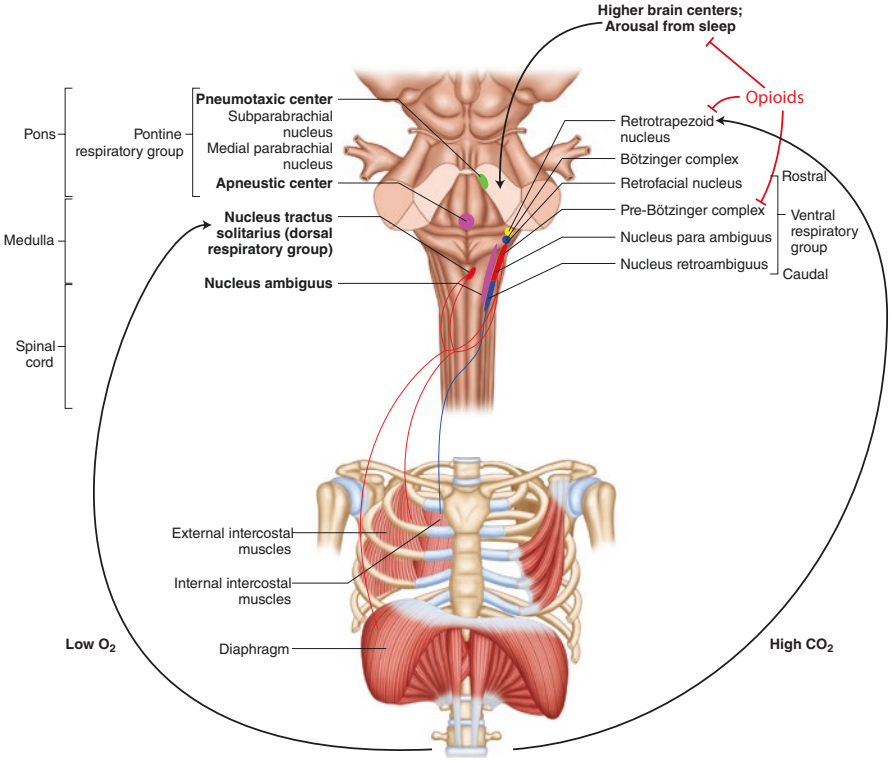


Fig. 2.5 The primary effect of chronic opioids appears to be an inhibition of the pre-Bötzinger complex, leading to irregular respiratory rhythm generation. Resulting low O_2 levels may lead to increased responses in the carotid body and nucleus tractus solitarius (NTS), augmenting hypoxic ventilatory responsiveness. Blunted responses to CO_2 are noted, along with elevated CO_2 levels in many individuals, although the level of this inhibition is unclear. Finally, it has been speculated that opioids may suppress arousal responses from sleep. *O_2* oxygen, *CO_2* carbon dioxide

Consequences

There are few studies examining the impact of CSA due to opioid use. Based on the shared manifestations of sleep disruption and oxyhemoglobin desaturation, the effects of O-CSA might be similar to those from other forms of CSA and from OSA, which includes cardiovascular and cerebrovascular morbidity, and metabolic syndrome. The presence of hypercapnia and sustained hypoxemia in many O-CSA may carry a risk of respiratory decompensation during medical illnesses or post-operatively. Notable other potential adverse effects include:

Neurocognitive Effects Excessive daytime sleepiness has been associated with opioid use but not specifically with O-CSA [9]. Similarly, withdrawal of opioids did not appear to decrease excessive sleepiness in one study, although residual sleep apnea remained present in most patients [25]. Nonetheless, compared to healthy controls, patients with O-CSA have substantially worse performance in psychomotor vigilance testing, a well-validated measure of attention, with the severity of impairment strongly correlated with severity of CSA [9].

Mortality The effect of O-CSA on mortality has not been well-examined. Data broadly examining the risk of chronic opioid use has not identified the presence of cardiorespiratory disorders in general to be a risk factor for mortality, although sample sizes in this group were small, and CSA was likely to be underdiagnosed [27].

Pain Potentially relevant for this population, sleep disruption and intermittent hypoxemia have been implicated in heightened pain sensitivity [28]. In our case example, it is notable that his opioid requirements were able to be weaned following effective ASV treatment and improvement in sleep continuity.

Treatment

The mainstay of therapy for O-CSA is a reduction in opioid dose to a level that minimizes or resolves respiratory events. However, this strategy is clearly not realistic for every patient, as in our case example. Alternative strategies include treatment with positive airway pressure devices. These interventions have only been assessed in physiological or short-term studies; long-term data regarding treatment of O-CSA is lacking. Furthermore, it is unclear which treatments might be effective in which patients; phenotyping techniques such as those used in patients with OSA are needed for personalizing treatment. Available therapeutic options are shown in Table 2.1 and include:

1. Reduction in opioid dose: Given the strong relationship between opioid dose and the development of CSA, opioid de-escalation is an appealing treatment strategy. Complete cessation of opioids results in the resolution of CSA, although clearly

Table 2.1 Comparison of different treatment strategies for O-CSA

Treatment	Description	Benefits	Downsides	Notes
Opioid dose reduction	Stopping or reducing dose of opioids, often under guidance of pain or addiction specialist	Highly effective	Not realistic in many patients	Unclear what degree of dose reduction is needed due to probable non-linear effect
CPAP	Continuous positive pressure via nasal/oronasal mask, as used for OSA	Inexpensive Simple to use	Unlikely to be effective in most patients	Not commonly used but may be preferable in more resource constrained settings
Supplemental oxygen	Often started in hospital or sleep laboratory settings when baseline saturation is low. Home use requires concentrator or tanks	Simple to titrate	Potential for worsening hypercapnia and persistence of respiratory events	Not recommended but encountered in practice due to under-recognition of O-CSA. Some patients may feel they need oxygen
Bilevel-ST	Applies inspiratory and expiratory pressure, along with a backup respiratory rate if apnea is detected	Effective at correcting hypoventilation	Relatively complex titration May not be effective at controlling apneas	Older modality but remains a mainstay of therapy for some patients
VAPS	Similar to bilevel-ST, but varies inspiratory pressure to achieve a target ventilation	May be most effective for control of hypoventilation May be better at controlling events than bilevel-ST	Newer mode with less familiarity Relatively complex titration	Newer modality, not reported in the literature for O-CSA
Adaptive servo-ventilation	Similar to above, but varies inspiratory pressure to maintain patient's current average ventilation	Most effective at controlling apneas	Does not correct hypoventilation	Often considered first-line treatment. Highly effective for many patients
AMPAkines	Drug that potentiates the effect of the neurotransmitter glutamate, which may counteract opioid effects on brainstem	Highly encouraging preliminary data	Not FDA approved	Unclear plans for further development

not all patients are able or willing to do so [25, 29]. The effect of reductions in opioid dose is less established. For example, it is unclear if halving the dose leads to a halving of CSA severity. The observation of particularly high CSA prevalence at morphine-equivalent doses above 100–200 mg/day might point to a threshold or non-linear effect [25, 14].

2. Continuous positive airway pressure: Although often thought of as a therapy for OSA, CPAP demonstrates some effect for the treatment of CSA, likely due to its effects on increasing lung volumes, improvement in oxygenation, and possibly washout of anatomic dead space, which may reduce hypercapnia. Nonetheless, the effectiveness for O-CSA is variable [30]. In one study, CPAP was effective in 54% of patients as first-line therapy [31]; however other studies have found a much lower effect, including no impact at all.
3. Supplemental oxygen: Supplemental oxygen has been shown to improve other forms of CSA, as well as certain patients with OSA. Although many patients with O-CSA exhibit severe desaturation and even daytime hypoxemia, the use of supplemental oxygen alone may not be appropriate based on the risk of hypoventilation, present in 45% of subjects by one estimate [9] (Fig. 2.3). Supplemental oxygen added to CPAP has been reported as a strategy for some patients [31], although longer-term outcomes are not established.
4. Non-invasive ventilation: The goal of ventilation is to stabilize breathing by preventing the development of apneas and potentially to augment ventilation. There are two types currently in use:

   (a) Bilevel ventilation with backup rate (bilevel-ST): Bilevel ventilation can be applied via a nasal or oronasal mask via a bedside device, similar to standard CPAP. Due to the presence of central apneas, a backup rate is needed; in our case example (Fig. 2.1), the use of bilevel without a backup rate may even worsen central apneas. Variable efficacy is reported; some studies have shown excellent response rates [32], while others demonstrate modest responses [33]. Given the complexity (i.e., settings for backup rate, trigger, cycle, and inspiratory times), the clinician, technologist, and sleep laboratory must be familiar with this modality. Volume-assured pressure support (VAPS) is a bilevel-ST modality that uses an algorithm to continuously adjust pressure to a target ventilation. This technology may offer some advantages to bilevel-ST but has not been examined in O-CSA.
   (b) Adaptive servo-ventilation: ASV is a bilevel-ST non-invasive ventilation device in which an algorithm adjusts the pressure support on a breath-to-breath basis, targeting a moving time-average ventilation (based on the patient's device-observed ventilation). The pressure support attenuates apneas and hypopneas, which thereby reduces subsequent ventilatory overshoots and ultimately eliminates ventilatory instability (case example –

Fig. 2.2). Most devices now incorporate an automatically adjusting expiratory positive airway pressure to stabilize the upper airway. Some studies of ASV have found suboptimal efficacy [7, 34], but a more recent study found resolution in all subjects [30]; differences might relate to advances in technology or severity of underlying CSA. Single night studies have found ASV to be superior to bilevel-ST in controlling the apnea-hypopnea index and with improvement in subjective sleep quality [33]. *Of note, ASV would not be expected to improve hypercapnia, unless the minimum pressure support settings are high enough to augment ventilation*.

5. Novel pharmacologic agents: Respiratory stimulants were previously used clinically in other conditions including chronic obstructive pulmonary disease, with limited efficacy and prominent side effects. Recently, a new class of compounds called AMPAkines have been investigated for the treatment of respiratory depression. These compounds modulate the AMPA receptor, lowering the threshold for activation by glutamate, its endogenous ligand. Animal studies have shown improvement in firing rate of mu-receptor agonist-treated pre-Bötzinger complex, as well as reversal of opioid-induced depression of respiratory rate. A phase IIa study in humans demonstrated that an AMPAkine prevented acute opioid-induced reductions in respiratory rate and carbon dioxide responsiveness, without an effect on heat pain tolerance [35]. Nonetheless, clinical data in central sleep apnea is not currently available, and these compounds are not yet FDA-approved.

Complex Sleep Apnea Due to Opioids

Although many patients with O-CSA have central apneas on diagnostic PSG, in others, central events only emerge following CPAP treatment for OSA [32]. This has been termed complex sleep apnea or CPAP-emergent sleep apnea, and while not every complex CSA is due to opioids, O-CSA should be a consideration when encountering residual or worsened respiratory events following the start of CPAP. In our case with a reported history of OSA, CPAP titration was associated with central apneas (Fig. 2.1).

Clinical Pearls

1. Opioid-induced central sleep apnea should be suspected in those using higher doses of any opioid, including intrathecal and partial opioid agonist preparations, and when concurrent sedatives are being used.
2. Although the consequences of O-CSA are not well established, diagnostic workup should be considered for those using opioids in the following scenarios: (1) unexplained hypoxemia or hypercapnia, (2) sleep-related complaints, (3) co-morbid cardiovascular/cerebrovascular or metabolic disease, and (4) as an adjunctive strategy to opioid reduction.

3. Reduction of opioid dose (and ideally complete cessation) is the mainstay of therapy for O-CSA. If not achievable, treatment with adaptive servoventilation, or alternatively bilevel-ST therapy, can be effective but requires familiarity on the part of the clinician and sleep laboratory.
4. O-CSA may be a reason for emergent central apneas in the OSA patient started on CPAP. A thorough medication and substance use history are thus needed in all such patients.

References

1. Levy B, Paulozzi L, Mack KA, Jones CM. Trends in opioid analgesic-prescribing rates by specialty, U.S., 2007-2012. Am J Prev Med. 2015;49(3):409–13.
2. Berterame S, Erthal J, Thomas J, Fellner S, Vosse B, Clare P, et al. Use of and barriers to access to opioid analgesics: a worldwide, regional, and national study. Lancet. 2016;387(10028):1644–56.
3. The use of opioids for the treatment of chronic pain. A consensus statement from the American Academy of Pain Medicine and the American Pain Society. Clin J Pain. 1997;13(1):6–8.
4. Rummans TA, Burton MC, Dawson NL. How good intentions contributed to bad outcomes: the opioid crisis. Mayo Clin Proc. 2018;93(3):344–50.
5. Hedegaard H, Warner M, Miniño A. Drug overdose deaths in the United States, 1999–2016. National Center for Health Statistics; 2017. Available from: https://www.cdc.gov/nchs/products/databriefs/db294.htm
6. International classification of sleep disorders. 3rd ed. Darien: American Academy of Sleep Medicine; 2014.
7. Farney RJ, Walker JM, Boyle KM, Cloward TV, Shilling KC. Adaptive servoventilation (ASV) in patients with sleep disordered breathing associated with chronic opioid medications for nonmalignant pain. J Clin Sleep Med. 2008;4(4):311–9.
8. Farney RJ, McDonald AM, Boyle K, Snow GL, Nuttall RT, Coudreaut MF, et al. Sleep disordered breathing (SDB) in patients receiving therapy with buprenorphine/naloxone. Eur Respir J. 2012;42:394–403.
9. Rose AR, Catcheside PG, McEvoy RD, Paul D, Kapur D, Peak E, et al. Sleep disordered breathing and chronic respiratory failure in patients with chronic pain on long term opioid therapy. J Clin Sleep Med. 2014;10(8):847–52.
10. Smith LA, Chong DW, Vennelle M, Denvir MA, Newby DE, Douglas NJ. Diagnosis of sleep-disordered breathing in patients with chronic heart failure: evaluation of a portable limited sleep study system. J Sleep Res. 2007;16(4):428–35.
11. Quintana-Gallego E, Villa-Gil M, Carmona-Bernal C, Botebol-Benhamou G, Martínez-Martínez Á, Sánchez-Armengol Á, et al. Home respiratory polygraphy for diagnosis of sleep-disordered breathing in heart failure. Eur Respir J. 2004;24(3):443–8.
12. Wang D, Teichtahl H, Drummer O, Goodman C, Cherry G, Cunnington D, et al. Central sleep apnea in stable methadone maintenance treatment patients. Chest. 2005;128(3):1348–56.
13. Filiatrault ML, Chauny JM, Daoust R, Roy MP, Denis R, Lavigne G. Medium increased risk for central sleep apnea but not obstructive sleep apnea in long-term opioid users: a systematic review and meta-analysis. J Clin Sleep Med. 2016;12(4):617–25.
14. Walker JM, Farney RJ, Rhondeau SM, Boyle KM, Valentine K, Cloward TV, et al. Chronic opioid use is a risk factor for the development of central sleep apnea and ataxic breathing. J Clin Sleep Med. 2007;3(5):455–61.
15. Webster LR, Choi Y, Desai H, Webster L, Grant BJ. Sleep-disordered breathing and chronic opioid therapy. Pain Med. 2008;9(4):425–32.

16. Jordan AS, O'Donoghue FJ, Cori JM, Trinder J. Physiology of arousal in obstructive sleep apnea and potential impacts for sedative treatment. Am J Respir Crit Care Med. 2017;196(7):814–21.
17. Caravita S, Faini A, Lombardi C, Valentini M, Gregorini F, Rossi J, et al. Sex and acetazolamide effects on chemoreflex and periodic breathing during sleep at altitude. Chest. 2015;147(1):120–31.
18. Sin DD, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. Am J Respir Crit Care Med. 1999;160(4):1101–6.
19. Gray K, Adhikary SD, Janicki P. Pharmacogenomics of analgesics in anesthesia practice: a current update of literature. J Anaesthesiol Clin Pharmacol. 2018;34(2):155–60.
20. Pattinson KT. Opioids and the control of respiration. Br J Anaesth. 2008;100(6):747–58.
21. Teichtahl H, Wang D, Cunnington D, Quinnell T, Tran H, Kronborg I, et al. Ventilatory responses to hypoxia and hypercapnia in stable methadone maintenance treatment patients. Chest. 2005;128(3):1339–47.
22. Hajiha M, DuBord M-A, Liu H, Horner RL. Opioid receptor mechanisms at the hypoglossal motor pool and effects on tongue muscle activity in vivo. J Physiol. 2009;587(11):2677–92.
23. Lorier AR, Funk GD, Greer JJ. Opiate-induced suppression of rat hypoglossal motoneuron activity and its reversal by ampakine therapy. PLoS One. 2010;5(1):e8766.
24. Ehsan Z, Mahmoud M, Shott SR, Amin RS, Ishman SL. The effects of anesthesia and opioids on the upper airway: a systematic review. Laryngoscope. 2016;126(1):270–84.
25. Schwarzer A, Aichinger-Hinterhofer M, Maier C, Vollert J, Walther JW. Sleep-disordered breathing decreases after opioid withdrawal: results of a prospective controlled trial. Pain. 2015;156(11):2167–74.
26. Horner RL, Hughes SW, Malhotra A. State-dependent and reflex drives to the upper airway: basic physiology with clinical implication. J Appl Physiol. 2013;116:325–36.
27. Bohnert AS, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, Ilgen MA, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA. 2011;305(13):1315–21.
28. Lam KK, Kunder S, Wong J, Doufas AG, Chung F. Obstructive sleep apnea, pain, and opioids: is the riddle solved? Curr Opin Anaesthesiol. 2016;29(1):134–40.
29. Davis MJ, Livingston M, Scharf SM. Reversal of central sleep apnea following discontinuation of opioids. J Clin Sleep Med. 2012;8(5):579–80.
30. Javaheri S, Harris N, Howard J, Chung E. Adaptive servoventilation for treatment of opioid-associated central sleep apnea. J Clin Sleep Med. 2014;10(6):637–43.
31. Chowdhuri S, Ghabsha A, Sinha P, Kadri M, Narula S, Badr MS. Treatment of central sleep apnea in U.S. veterans. J Clin Sleep Med. 2012;8(5):555–63.
32. Guilleminault C, Cao M, Yue HJ, Chawla P. Obstructive sleep apnea and chronic opioid use. Lung. 2010;188(6):459–68.
33. Cao M, Cardell CY, Willes L, Mendoza J, Benjafield A, Kushida C. A novel adaptive servoventilation (ASVAuto) for the treatment of central sleep apnea associated with chronic use of opioids. J Clin Sleep Med. 2014;10(8):855–61.
34. Ramar K, Ramar P, Morgenthaler TI. Adaptive servoventilation in patients with central or complex sleep apnea related to chronic opioid use and congestive heart failure. J Clin Sleep Med. 2012;8(5):569–76.
35. Oertel BG, Felden L, Tran PV, Bradshaw MH, Angst MS, Schmidt H, et al. Selective antagonism of opioid-induced ventilatory depression by an ampakine molecule in humans without loss of opioid analgesia. Clin Pharmacol Ther. 2010;87(2):204–11.

Chapter 3
Sleep Apnea and Stroke

K. Nicole Mims and Douglas B. Kirsch

Case Presentation

An 80-year-old gentleman presents for evaluation of sleepiness. His symptoms started many years ago, and he was diagnosed with obstructive sleep apnea (OSA) initially in the 1980s. He started continuous positive airway pressures (CPAP) at that time and continued to use CPAP with a full-face mask at a pressure of 14 cmH_2O. He uses CPAP nightly. He has noticed increased awakenings in the last several months and wonders if the machine is working adequately. He also hasn't received CPAP supplies in over a year. He feels less rested in the morning now than when he first started CPAP. His wife notices that he dozes more frequently during the day. She describes him as having a "button in his butt" so that when he sits down, he "shuts off" and falls asleep. She restricts him from driving because of his propensity for falling asleep while sitting. He doesn't use sleep aids. He denies complaints of leg movements or leg discomfort, vivid dreams, or dream enactment. His son and daughter are also concerned about his memory over the last few years.

Notably, his past medical history includes coronary artery disease, atrial flutter, hyperlipidemia, and diabetes. He also had a left pontine stroke approximately 18 months prior to his visit. He has minimal residual weakness from the stroke, including no dysphagia or dysarthria.

His most recent sleep study from 2009 revealed an overall apnea-hypopnea index (AHI) of 54 events/h. He had 20 mixed apneas and 7 central apneas; most of the respiratory events were obstructive apneas and hypopneas. His oxygen nadir was

K. N. Mims
Atrium Health, Charlotte, NC, USA

D. B. Kirsch (✉)
Atrium Health, UNC School of Medicine, Charlotte, NC, USA

C. Won (ed.), *Complex Sleep Breathing Disorders*,
https://doi.org/10.1007/978-3-030-57942-5_3

70%. The periodic limb movement index was 0 events/h. He received a CPAP with a pressure of 14 cmH_2O, and his CPAP download from 3 years ago showed an AHI of 4 events/h on the machine. However, the download from his current visit showed an AHI of 42 events/h on the same settings. Central apnea data could not be ascertained on the device download, due to the era of the machine.

His machine was capable of auto-titration positive airway pressure (APAP), so his settings were changed to 5–20 cmH_2O. The following 30-day download showed an AHI of 45 events/h. His pressure was then changed to 10 cmH_2O with little change in download-reported AHI. An in-laboratory titration study was ordered, testing CPAP pressures between 5 and 18 cmH_2O and bilevel positive airway pressure (BPAP) pressures between 8/5 and 18/14 cmH_2O. All pressures were ineffective due to persistent obstructive and treatment-emergent central apneas. A representative selection of the polysomnogram can be seen in Fig. 3.1. At this point, a BPAP to adaptive servo-ventilation (ASV) titration was ordered showing inadequate BPAP pressures and improvement with the ASV pressure tried. An ASV device was ordered at that time with settings of expiratory pressure (EPAP) minimum of 8 cmH_2O, EPAP maximum of 25 cmH_2O, maximum pressure of 25 cmH_2O, pressure support minimum of 0, and pressure support maximum of 14 cmH_2O with auto-backup breathing rate. On ASV, his AHI reduced to seven events/h (as seen in Fig. 3.2). After starting ASV, he noted improvement in his sleep quality, and he felt more rested upon awakening. His wife also noticed he was less drowsy during the day and didn't doze when sitting down. He tolerates the ASV pressures well.

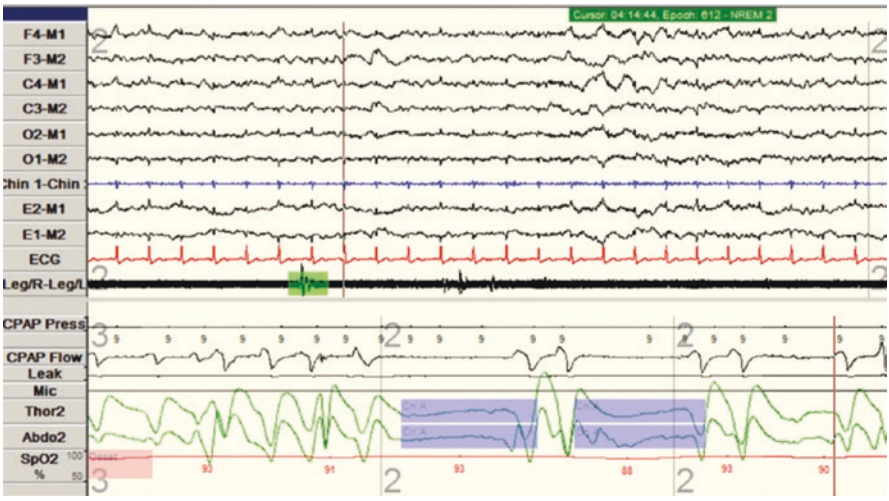


Fig. 3.1 In-lab polysomnography demonstrating central apneas while on PAP therapy

Average EPAP	6.2 cmH2O
Average Pressure Support	3.6 cmH2O
90% of the time device EPAP pressure was <=	6.5 cmH2O
90% of the time device Pressure Support was <=	8.1 cmH2O
Average Percent of Night in Periodic Breathing	17.5%
Average Time in Large Leak Per Day	0 secs.
Average Percent Night in Large Leak	0.0%
Average Breath Rate	16.5 bpm
Average Minute Vent	5.7
Average AHI	7.0

Fig. 3.2 Download data from ASV demonstrating adequate therapy with pressure settings

Discussion

Sleep-disordered breathing (SDB) is very common in pre- and post-stroke patients and is often obstructive in nature [1]. In patients who have had a stroke, the prevalence of sleep-disordered breathing is estimated at 38% for AHI > 20 events/h and 72% for AHI > 5 events/h, with only 7% having central sleep apnea (CSA) [2]. The prevalence of OSA may be higher in more severe strokes; for example, a study that prospectively evaluated sleep apnea in patients receiving thrombolysis for stroke found that 96% of patients receiving thrombolysis had an AHI > 5 events/h [3]. The occurrence of CSA and Cheyne-Stokes breathing (CSB) varies depending upon the timing after stroke [4]. A few studies have shown that in the initial days after a stroke, CSB is frequent. Risk factors for CSB post-stroke include older age, stroke severity/size, and left ventricular dysfunction [5]. More often, immediate post-stroke patients present with complex SDB involving a combination of obstructive and central respiratory events. The evolution of SDB following a stroke is unclear. CSA has been described to improve within 3 months after an acute stroke [6, 7]; OSA has been described to either remain stable [2] or to decrease in severity with time [8].

Pathogenesis

Stroke may cause or worsen pre-existing SDB through several mechanisms. These include dysfunctional upper airway neuromuscular control, respiratory muscle weakness due to supra- or infra-tentorial strokes, and altered ventilatory stability or carbon dioxide (CO_2) sensitivity in patients with medullary or other brainstem lesions [9]. Other factors could also contribute to SDB, including hypoxemia due to atelectasis, paralysis, forced supine position, medications, and sleep fragmentation due to stress or pain. As many as 40% of ischemic stroke patients have pharyngeal muscle and hypoglossal nerve dysfunction, which may contribute to upper airway

obstruction [10]. Furthermore, stroke patients are often forced into prolonged supine body position, which may exacerbate positional OSA in 25% of stroke patients [11].

The literature on stroke size and location and the occurrence of SDB is limited and mixed. The medulla oblongata plays a primary role in respiratory control through central chemoreceptors that affect respiratory loop gain. Lesions to the respiratory centers within the medulla have shown to decrease chemosensitivity during wakefulness and sleep and may contribute to SDB [9]. Those with infratentorial lesions of the brainstem and cerebellum have greater AHI than those with cortical strokes [12]. Likewise, another study showed greater CSA and nocturnal desaturations in those with brainstem compared to cortical strokes [13]. In contrast, Siccoli et al. found that patients who have total anterior circulation strokes have greater AHI (with 40% of AHI comprised of CSA) than infarcts to other brain regions [5]. Strokes in the pons, a part of the midbrain, was also noted to be associated with high AHI, but with only 12% of events consisting of CSA. Cerebral edema, regardless of lesion location, may also contribute to occurrence of SDB by precipitating hypocapnia and unstable loop gain. These studies support a central process to the pathogenesis of sleep-disordered breathing. However, it is probably too early to conclude any association between stroke size/location and SDB; this information does not reliably inform us of the optimal mode of therapy for a particular patient.

Assessment and Diagnosis

SDB after stroke is considered as a potential modifiable risk factor. Patients suffering from OSA in neurologic rehab after stroke show more cognitive impairment in attention, executive functioning, visual perception, psychomotor ability, intelligence, and neurological status and activities of daily living [14]. OSA also contributes to cardiovascular stress and morbidity and mortality via multiple modalities including hypertension, increased inflammation, endothelial damage, and arrhythmias. Based on strong evidence of reduced cardiovascular burden when sleep apnea is treated, the American Heart Association (AHA) and American Stroke Association (ASA) recommend patients who have had a stroke and/or transient ischemic attack (TIA) with symptoms suggestive of sleep apnea undergo a sleep study for evaluation of sleep-disordered breathing [15].

In an American Academy of Sleep Medicine (AASM) practice guideline from 2017, polysomnography instead of home sleep apnea testing was recommended to diagnose patients with significant medical comorbidities including history of stroke [16]. This recommendation was based on lack of data supporting adequate diagnosis in patients with comorbidities and history of stroke.

In the patient case, initial diagnostic testing was completed prior to patient's stroke. However, the patient's APAP data download post-stroke indicated insufficient efficacy of positive airway pressure (PAP) therapy. A repeat PAP therapy titration is the most appropriate next step to determine appropriate pressure settings and

further evaluate non-obstructive breathing difficulties. Repeating a diagnostic study would have limited clinical usefulness since there is little question the patient has sleep-disordered breathing. In some patient cases, reported efficacy by AHI-based download can be inaccurate, and in-lab polysomnography PAP titration can be used to verify or clarify reported efficacy by the PAP device. Occasionally, our group will use overnight pulse oximeters on PAP therapy to assess desaturations as an indicator of airway patency as a more convenient and fiscally reasonable alternative to in-lab polysomnography, although the merits of this testing are clinically valued rather than driven by research criteria. Additionally, oximetry will not gauge whether respiratory events are obstructive or central, solely demonstrating drops in oximetry suggestive of sleep-disordered breathing. In the Continuous Positive Airway Pressure for Central Sleep Apnea and Heart Failure (CANPAP) trial, CPAP at 10 cmH_2O was effective in reducing residual central events seen with PAP therapy, at least in heart failure patients [17]; thus this was part of this patient's treatment strategy.

Treatment of Sleep-Disordered Breathing

Once the correct diagnosis is determined, treatment for OSA often consists of using PAP therapy to maintain airway patency. Although SDB may reduce or resolve in many patients over time in conjunction with functional recovery after stroke, SDB can significantly hinder post-stroke rehabilitation. The few studies that have examined the therapeutic effect of CPAP on recovery outcomes in stroke patients have reported significantly faster functional recovery, reduced hospitalization time, and reduced frequency of re-hospitalization. This supports treating acute post-stroke SDB to improve immediate and long-term clinical outcomes.

The AHA/ASA recently published recommendations suggesting treatment of sleep apnea in stroke/TIA patients to reduce cardiovascular burden [15]. A study by Para et al. identified improvement in long-term survival in ischemic stroke patients with moderate-severe OSA who utilized nasal CPAP compared to those who did not [18]. Furthermore, a prospective study by Aaronson et al. assigned stroke patients with sleep apnea to PAP therapy and sham PAP therapy groups and found improvement in cognitive functioning in the treated group, although no significant difference was observed in activities of daily living between the two groups [19].

If central apneas are prevalent during PAP therapy titrations, an ASV titration may be indicated (see below). Alternatively, if PAP-emergent central sleep apnea is suspected, studies indicate use of CPAP therapy over a few months may result in resolution of PAP-emergent central sleep apnea in two-thirds of cases [20]. Thus, if central apneas emerge with PAP therapy, further titration studies and switching forms of therapy may not be necessary in all cases, depending on the clinical situation and available data.

Another form of PAP therapy is bilevel positive airway pressure, utilized in patients with comorbid hypoventilation conditions, patients intolerant of higher CPAP pressures, and patients with complex or central sleep apnea (though it is not

always more effective for central apnea) [21]. One will need to be attentive to trigger and cycle sensitivity settings on BPAP, since a stroke patient may have weak respiratory muscles leading to ineffective triggering or cycling of pressures, resulting in BPAP desynchrony and discomfort. The use of a backup rate with BPAP depends on the underlying SDB pattern. If there is predominantly obstructive apneas or hypoventilation/hypopneas, BPAP in spontaneous mode (BPAP-S) may suffice. However, if there are predominantly central apneas of long durations, then BPAP in timed mode (BPAP-T) with backup rate may be appropriate.

Some notable limitations to PAP therapy include poor tolerance of the device and equipment, cognitive impairment, and financial burden. There are significant challenges to using PAP in the acute setting due to the disabling impact of stroke [8]. Studies indicate about 50% of patients demonstrate adherence with PAP therapy when followed for 5 years, with adherence defined as exceeding 70% of days PAP therapy is used greater than 4 h over a consecutive 30-day period. Comparatively, adherence in stroke patients tends to be significantly lower based on research data; Bassetti et al. observed only 31% adherence in stroke patients at 5 years [7]. Identifying the etiology of decreased adherence in patients who have had a stroke is challenging. The Bassetti study also tracked daytime sleepiness as measured by the Epworth Sleepiness Scale (ESS); the ESS did not seem to correlate with long-term PAP use. Aphasia and severity of motor disability predicted poor PAP adherence in another study of stroke patients, suggestive that more severe motor and cognitive dysfunction post-stroke may prove to be a barrier in utilizing PAP therapy in this patient population [22].

Incidence of primary central apnea in stroke patients was 8% based on a systemic review [23]. In the past, central sleep apnea syndromes were thought to respond better to BPAP or ASV therapy; however, as mentioned, PAP-emergent central sleep apnea, defined by emergence of central apnea with use of PAP therapy, tends to resolve spontaneously in all but 1/3 of cases, which comprises 3% of all OSA patients treated with PAP therapy [20]. It should be noted however that these studies were not conducted in post-stroke patients, so whether this is generalizable to this population is unknown. Persistence of PAP-emergent central sleep apnea is associated with decreased PAP adherence compared to patients who experience resolution of the therapeutically induced central apneas [20]. One hypothesis for development of central sleep apnea is lability of CO_2 reservoir and apnea threshold based on underlying comorbidities. In reflecting back to the case above, this patient's brainstem stroke may have affected his baseline apnea threshold, thus increasing his risk for central sleep apnea. In this case, the patient's PAP-emergent CSA did not resolve spontaneously with regular PAP use.

ASV delivers servo-controlled inspiratory pressure support on top of expiratory positive airway pressure and was developed to treat CSA. However, based on data from the SERVE-HF study which evaluated ASV use in patients with central sleep apnea and systolic heart failure, ASV should be avoided in patients with cardiac ejection fractions below 45% because of increased risk for cardiovascular mortality [24]. Clinical trials evaluating outcomes of ASV use in patients with CSA related to stroke have not occurred as of the writing of this chapter.

Alternatives to PAP therapy for treatment of OSA include oral appliances and surgery. Surgical options for sleep apnea include several surgeries to improve airway patency.

Alternative therapies related to central sleep apnea include nocturnal oxygen, acetazolamide, and theophylline. The above therapies are included in the CSA treatment guidelines published by the AASM, all of which are recommended in the setting of central sleep apnea related to congestive heart failure [25]. These therapies have not been widely studied in stroke patients. Nocturnal oxygen therapy has been evaluated as an alternative therapy to PAP for sleep-disordered breathing in stroke patients, but while it reduces oxygen desaturations, it appears to prolong apneic events [26].

Due to the complexity of stroke-related SDB, phenotyping techniques for different observed patterns and propensities of sleep-breathing disorders are being developed which would allow for precision medicine and tailored therapies. These new phenotyping and therapy developments together with understanding stroke location/size and functional impact could provide important clinical information about drivers of post-stroke SDB for an individual and optimize SDB treatment.

Clinical Pearls

- Sleep apnea and stroke are commonly associated, with sleep apnea associated with negative outcomes in patients who have had a stroke.
- Treating sleep apnea post-stroke acutely and chronically can improve recovery and functionality, though treatment may be challenging in this patient population due to stroke-related symptoms.
- Emergence of central apneas may occur post-stroke; thus treatment strategies may require close patient monitoring and more complex forms of PAP therapy such as ASV or BPAP.
- Most recommended guidelines for treatment of primary central apneas or treatment-emergent central apneas are derived from studies in non-stroke patients.

References

1. Heinzer R, Vat S, Marques-Vidal P, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med. 2015;3(4):310–8.
2. Johnson KG, Johnson DC. Frequency of sleep apnea in stroke and TIA patients: a meta-analysis. J Clin Sleep Med. 2010;6(2):131–7.
3. Huhtakangas JK, Huhtakangas J, Bloigu R, Saaresranta T. Prevalence of sleep apnea at the acute phase of ischemic stroke with or without thrombolysis. Sleep Med. 2017;40:40–6.
4. Stevens D, Martins RT, Mukherjee S, Vakulin A. Post-stroke sleep-disordered breathing-pathophysiology and therapy options. Front Surg. 2018;5:9.

5. Siccoli MM, Valko PO, Hermann DM, Bassetti CL. Central periodic breathing during sleep in 74 patients with acute ischemic stroke - neurogenic and cardiogenic factors. J Neurol. 2008;255(11):1687–92.
6. Parra O, Arboix A, Bechich S, et al. Time course of sleep-related breathing disorders in first-ever stroke or transient ischemic attack. Am J Respir Crit Care Med. 2000;161(2 Pt 1):375–80.
7. Bassetti CL, Milanova M, Gugger M. Sleep-disordered breathing and acute ischemic stroke: diagnosis, risk factors, treatment, evolution, and long-term clinical outcome. Stroke. 2006;37(4):967–72.
8. Bravata DM, Concato J, Fried T, et al. Continuous positive airway pressure: evaluation of a novel therapy for patients with acute ischemic stroke. Sleep. 2011;34(9):1271–7.
9. Morrell MJ, Heywood P, Moosavi SH, Guz A, Stevens J. Unilateral focal lesions in the rostro-lateral medulla influence chemosensitivity and breathing measured during wakefulness, sleep, and exercise. J Neurol Neurosurg Psychiatry. 1999;67(5):637–45.
10. Brown DL, Chervin RD, Wolfe J, et al. Hypoglossal nerve dysfunction and sleep-disordered breathing after stroke. Neurology. 2014;82(13):1149–52.
11. Camilo MR, Fernandes RM, Sander HH, et al. Supine sleep and positional sleep apnea after acute ischemic stroke and intracerebral hemorrhage. Clinics (Sao Paulo). 2012;67(12):1357–60.
12. Bassetti C, Aldrich MS, Quint D. Sleep-disordered breathing in patients with acute supra- and infratentorial strokes. A prospective study of 39 patients. Stroke. 1997;28(9):1765–72.
13. Brown DL, McDermott M, Mowla A, et al. Brainstem infarction and sleep-disordered breathing in the BASIC sleep apnea study. Sleep Med. 2014;15(8):887–91.
14. Aaronson JA, van Bennekom CA, Hofman WF, et al. Obstructive sleep apnea is related to impaired cognitive and functional status after stroke. Sleep. 2015;38(9):1431–7.
15. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45(7):2160–236.
16. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2017;13(3):479–504.
17. Bradley TD, Logan AG, Kimoff RJ, et al. Continuous positive airway pressure for central sleep apnea and heart failure. N Engl J Med. 2005;353(19):2025–33.
18. Parra O, Sanchez-Armengol A, Capote F, et al. Efficacy of continuous positive airway pressure treatment on 5-year survival in patients with ischaemic stroke and obstructive sleep apnea: a randomized controlled trial. J Sleep Res. 2015;24(1):47–53.
19. Aaronson JA, Hofman WF, van Bennekom CA, et al. Effects of continuous positive airway pressure on cognitive and functional outcome of stroke patients with obstructive sleep apnea: a randomized controlled trial. J Clin Sleep Med. 2016;12(4):533–41.
20. Nigam G, Riaz M, Chang ET, Camacho M. Natural history of treatment-emergent central sleep apnea on positive airway pressure: a systematic review. Ann Thorac Med. 2018;13(2):86–91.
21. Kushida CA, Littner MR, Hirshkowitz M, et al. Practice parameters for the use of continuous and bilevel positive airway pressure devices to treat adult patients with sleep-related breathing disorders. Sleep. 2006;29(3):375–80.
22. Wessendorf TE, Wang YM, Thilmann AF, Sorgenfrei U, Konietzko N, Teschler H. Treatment of obstructive sleep apnoea with nasal continuous positive airway pressure in stroke. Eur Respir J. 2001;18(4):623–9.
23. Dong R, Dong Z, Liu H, Shi F, Du J. Prevalence, risk factors, outcomes, and treatment of obstructive sleep apnea in patients with cerebrovascular disease: a systematic review. J Stroke Cerebrovasc Dis. 2018;27(6):1471–80.
24. Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. N Engl J Med. 2015;373(12):1095–105.
25. Aurora RN, Chowdhuri S, Ramar K, et al. The treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses. Sleep. 2012;35(1):17–40.
26. Mehta V, Vasu TS, Phillips B, Chung F. Obstructive sleep apnea and oxygen therapy: a systematic review of the literature and meta-analysis. J Clin Sleep Med. 2013;9(3):271–9.

Chapter 4
Obstructive and Central Sleep Apnea Treatment Challenges in Atrial Fibrillation

Sunjeet Kaur and Reena Mehra

Case History and Examination

The patient is a 63-year-old male with history of hypertension, hyperlipidemia, type 2 diabetes mellitus, chronic kidney disease stage 3, nephrolithiasis, gastroesophageal reflux disease, and obesity who presents with snoring, fatigue, and daytime sleepiness.

Daytime sleepiness has limited his activity level and ability to enjoy time with his family. He has limited his driving given concern for drowsy driving. He has a regular sleep/wake schedule. He goes to bed at 9 PM and wakes up at 6:30 AM with an alarm. He has no problem falling asleep, but has recurrent awakenings throughout the night. He does not feel refreshed when he wakes up. He feels that overall he gets only 5 h of sleep in a 24 h period. He takes about 2–3 naps every day. Naps ranged from 15 to 60 min. The patient does not feel refreshed after the naps. He prefers to sleep on his side and has been told that he snores. His family members have noticed that he stops breathing during his sleep. He himself has experienced waking up choking or gasping for air. He denies history of head injury or prolonged viral illness. He denies any symptoms related to restless legs syndrome, parasomnias, or seizures.

Electronic Supplementary Material The online version of this chapter (https://doi.org/10.1007/978-3-030-57942-5_4) contains supplementary material, which is available to authorized users.

S. Kaur
Case Western Reserve University Metro Health, Cleveland, OH, USA

R. Mehra (✉)
Department of Sleep Medicine, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA
e-mail: mehrar@ccf.org

C. Won (ed.), *Complex Sleep Breathing Disorders*,
https://doi.org/10.1007/978-3-030-57942-5_4

He denies smoking or drug use. He drinks alcohol socially – on average once a month. He has noticed that his sleep is more fragmented on nights he consumes alcohol. Family history is significant for his father who has sleep apnea, although he never used positive airway pressure (PAP) therapy. Also, both of his parents had atrial fibrillation (AF).

On examination, the patient is afebrile, blood pressure 179/90 mm Hg, heart rate 65/min, and respiratory rate 18/min. The patient's body mass index is 35 kg/m^2 and neck circumference 45 cm. Upper airway examination reveals Friedman tongue position of 3, Mallampati class 4, and tonsils grade 1. Nasal congestion with valve incompetence is noted along with overbite. Heart sounds are regular. No murmur is noted. Lungs are clear to auscultation with no added sounds. No peripheral edema was noted. Patient was well oriented with no neurological deficit. The patient was anxious and irritable due to poor sleep quality. His Epworth sleepiness scale (ESS) score was 13.

Medications include lisinopril, hydrochlorothiazide, amlodipine, atorvastatin, omeprazole, and metformin.

Evaluation

Patient underwent home sleep apnea testing which confirmed the diagnosis of severe obstructive sleep apnea syndrome. There was a total of 414 respiratory events. Of these events, the total number of apneas was 165 (155 obstructive, 1 mixed, and 9 central) and 249 hypopneas. Respiratory event index was 50.4. The mean oxygen saturation during the study was 90.0%, with a minimum oxygen saturation of 77.0%. The patient spent 37.3 min at oxygen saturation measured less than 90% (7.6% of recording time) and 13.5 min at oxygen saturation measured at or less than 88% (2.7% of recording time). The average heart rate was 84 bpm with a range of 38–250 bpm. Given the portable nature of the study, it was unclear whether the elevation in heart rate was based upon artifact.

This was followed by in-lab positive airway pressure titration study where none of the tested CPAP/bilevel PAP settings normalized the apnea-hypopnea index. Titration was started at CPAP of 5 cm H_2O and then transitioned to bilevel PAP due to emergence of central apneas. Bilevel PAP settings ranging from 11/7 to 14/10 cm H_2O were tested. None of the settings normalized the apnea-hypopnea index (AHI). Patient was recommended to come back for in-lab titration study starting from bilevel PAP 12/8 cm H_2O and up-titrating as needed. There were frequent central respiratory events with a Cheyne-Stokes breathing observed throughout the study consistent with treatment-emergent central sleep apnea. Newly diagnosed AF was present in the first half hour and the last 4 h of the sleep study (Figs. 4.1 and 4.2). It was recommended that the patient should return for a full night bilevel PAP titration study starting with 12/8 cmH_2O and also to consider a formal workup for AF since there is no mention of this arrhythmia in the patient's medical record (Fig. 4.3).

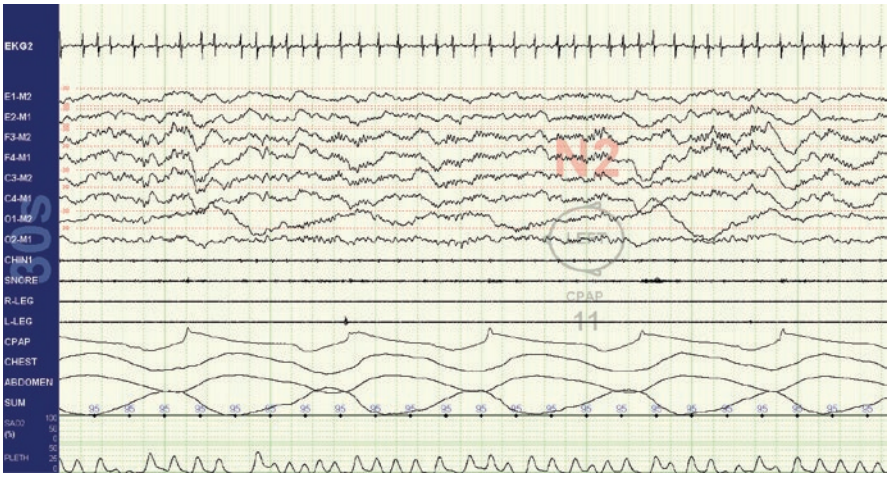


Fig. 4.1 30 s epoch showing atrial fibrillation

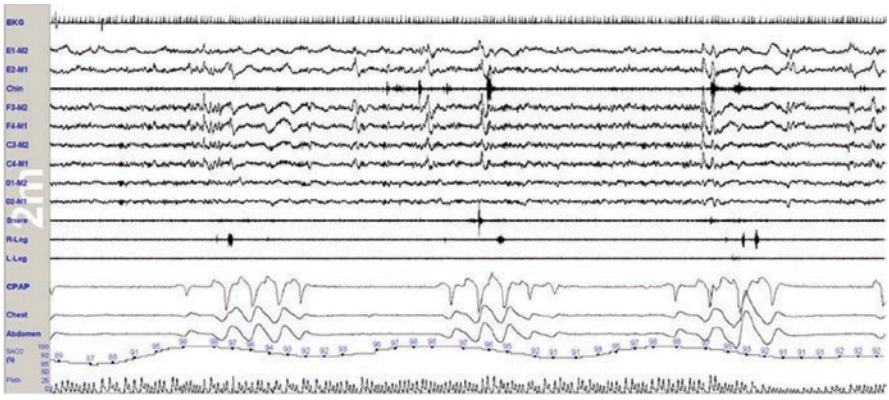


Fig. 4.2 2 min epoch showing atrial fibrillation and apnea episodes

Cardiology referral was placed and echocardiogram showed ejection fraction of 57 ± 5%. Right ventricle was mildly dilated with estimated right ventricular pressure of 33 mm Hg and estimated right atrial pressure of 5 mmHg. Video 4.1 shows active AF on the echocardiogram.

A second PAP titration study showed that the patient did best at a bilevel PAP setting of 19/12 cmH_2O with a back-up rate of 12 breaths/min. AHI at this setting was 2.7 with no central apneas. At this setting, snoring was eliminated and the average oxygen saturation was 94% (oxygen saturation nadir of 88%). Bilevel PAP 19/12 cmH_2O with humidification and a back-up rate of 12 breaths/min was recommended.

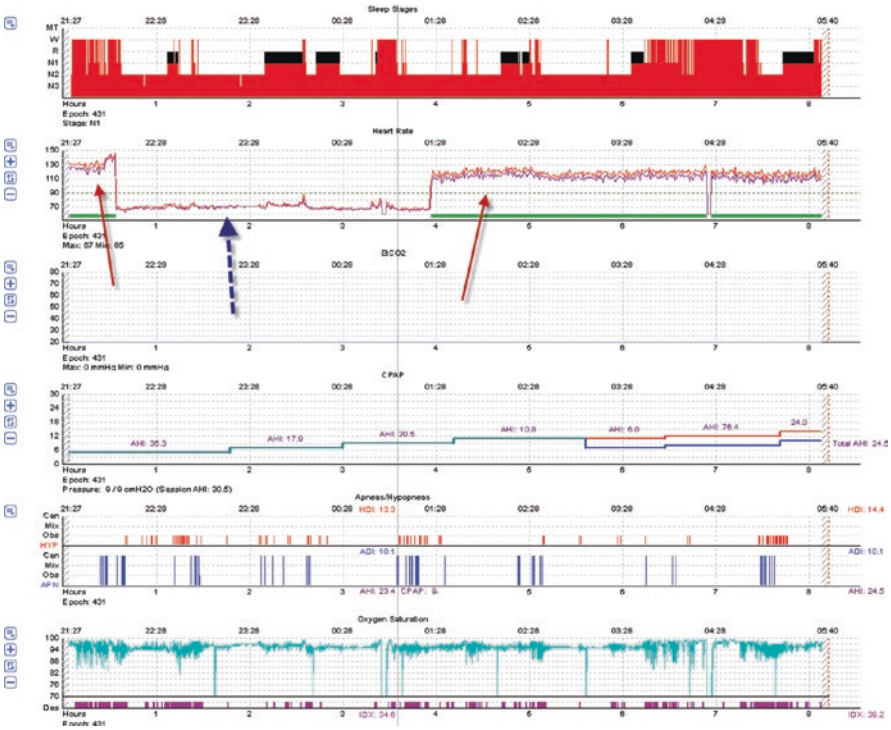


Fig. 4.3 Hypnogram from initial positive airway pressure (PAP) titration study. Atrial fibrillation with increased heart rate was noted in the first half hour and the last 4 h of the sleep study with persistence of respiratory events despite use of PAP therapy

Diagnosis

Diagnosis of obstructive and central sleep apnea along with AF was made.

Outcome

The patient was started on bilevel PAP at 19/12 cm H_2O with back-up rate of 12 breaths/min. The patient initially had issues with mask leak, but with proper mask fitting, he responded very well. The patient's symptoms of daytime sleepiness improved markedly (ESS post-therapy decreased from 13 to 8). The patient was evaluated by cardiology and started on flecainide 100 mg – one tablet by mouth every 12 h – and eventually underwent cardioversion. He was also started on anti-coagulation with dabigatran 150 mg capsule daily. Cardioversion was successful in conversion to normal sinus rhythm.

The patient continues to be compliant with bilevel PAP use and no recurrence of AF was noted. Data download from bilevel PAP machine showed that patient was using machine for >80% of nights and on an average >6 h per night. Also, the AHI with the current pressure settings was well controlled with an average AHI over 30-day period of 2.8.

Discussion

Introduction

AF is the most prevalent sustained cardiac arrhythmia. Epidemiological studies have shown increase in overall burden, incidence, and prevalence of AF. There also has been an increase in mortality associated with AF. Globally, 20.9 million men and 12.6 million women are estimated to have AF in 2010 [1]. This leads to huge economic implications. Disability-adjusted life years related to AF increased ~18% from 1990 to 2010 [1]. It is estimated that AF accounts for about $16–26 billion of annual US expense [2]. Part of the increase in AF is attributable to increasing age and obesity; however, there is a proportion of risk which remains unexplained [3]. Exact reasons for increase in AF incidence and prevalence are not known. There is a possibility that sleep apnea could be contributing in part to this trend.

As approximately one third of patients with AF are asymptomatic [4], this case highlighted the unique opportunity to diagnose previously unrecognized AF during routine diagnostic polysomnography (Table 4.2). For example, a study in heart failure patients with cardiac resynchronization therapy has shown that of 100 patients assumed to be in sinus rhythm, 27% were found to have paroxysms of AF [5].

OSA is very common in the general population and is associated with substantial morbidity and mortality. About 17% of the general adult population has OSA [6], and this prevalence is increasing with the obesity epidemic. It is estimated that about 1 in 5 adults have mild OSA, and 1 in 15 adults have moderate to severe OSA [6]. Approximately 85% of cases are estimated to be undiagnosed [7]. OSA is characterized by repetitive complete or partial collapse of the upper airway during sleep, resulting in an apneic or hypopneic event, respectively [8]. Obstructive episodes are characterized by closure of the upper airway and by progressively increasing respiratory efforts, culminating in an arousal from sleep and a reopening of the airway. People who are susceptible to OSA typically have a smaller, more collapsible airway which is less distensible and has a higher critical closing pressure [9].

OSA and AF share multiple risk factors. Some of these include hypertension, congestive heart failure, male gender, and coronary artery disease [10]. The rising prevalence of obstructive sleep apnea is directly related to BMI albeit additional explanatory risk factors also play a role [11]. A meta-analysis of population-based cohort studies have shown that obese individuals have 49% increased risk of developing AF and this risk increases in parallel with BMI [12].

Epidemiology and Clinic-Based Studies Characterizing the Relationship of Sleep Apnea and Atrial Fibrillation

Multiple studies have emphasized the role of OSA as potential modifiable risk factor for cardiac arrhythmias, especially AF. The prevalence of AF and OSA increases with age and BMI. The direct association of AF and OSA was observed during study involving retrospective analysis of adults referred for an initial polysomnogram and development of AF during follow-up [13]. Decrease in nocturnal saturation was observed to be a strong predictor for new-onset AF development [13]. OSA has been shown to be arrhythmogenic. A higher risk of hospitalization and more severe symptomatology has been seen in AF patients with OSA compared to those without [14].

The Sleep Heart Health Study showed increased likelihood of AF in patients with sleep-disordered breathing (SDB) [15]. Increased severity of SDB, whether obstructive or central events, was shown to increase odds of AF [16]. Another analysis from the Sleep Heart Health Study suggests a temporal relationship between sleep-disordered breathing and discrete episodes of arrhythmia, i.e., paroxysms of AF. There was increased arrhythmia risk in the 90 seconds following a respiratory disturbance when compared to following normal breathing [17]. Data from the Sleep Heart Health Study also demonstrated central sleep apnea (CSA) to be associated with incident AF. The odds of developing AF were shown to be increased by 2–3 fold in patients with CSA. CSA was defined by a central apnea index of ≥5, or by the presence of Cheyne-Stokes respiration (CSR) (Table 4.1) [16].

The outcomes of sleep disorders in older men (MrOS Sleep) study, an epidemiologic cohort or community-dwelling older men, showed that increasing severity of sleep apnea was associated with progressive increase in odds of AF [18]. CSA was shown to be associated with approximately threefold increased odds of AF, and CSR-CSA (Cheyne-Stokes respiration - central sleep apnea) was associated with fivefold increase in odds of AF [18].

Table 4.1 International Classification of Sleep Disorders (ICSD-3) diagnostic criteria for Central Sleep Apnea with Cheyne-Stokes breathing

Diagnostic criteria [8]
(A/B) + C + D meet diagnostic criteria
A. The presence of one or more of the following (excessive daytime sleepiness, snoring, witnessed apnea, shortness of breath upon awakening and difficulty of sleep initiation or maintenance, multiple awakening, or nonrestorative sleep)
B. Congestive heart failure, neurological disorder, or atrial fibrillation
C. Polysomnography (during diagnostic or positive airway pressure titration) shows all of the following: Five or more central apneas and/or central hypopneas per hour of sleep The total number of central apneas and/or central hypopneas is >50% of the total number of apneas and/or hypopneas The pattern of ventilation meets criteria for Cheyne-stokes breathing (CSB)
D. The disorder is not better explained by other sleep disorders, medications, or substance use

Table 4.2 The American Academy of Sleep Medicine ECG scoring rules [54]

ECG pattern	AASM scoring rules
Sinus tachycardia	Sustained heart rate >90 beats per minute (bpm) in adults
Sinus bradycardia	Sustained heart rate <40 bpm ≥ age 6 years[a]
Cardiac asystole	Cardiac pauses lasting >3 s > age 6 years
Wide complex tachycardia	Heart rate > 100 bpm with QRS >0.12 s, > 3 consecutive beats
Narrow complex tachycardia	Heart rate > 100 bpm with QRS <0.12 s, > 3 consecutive beats
Atrial fibrillation	Irregularly irregular ventricular rhythm with P waves consistently replaced by rapid oscillation which vary in size, shape, and timing

Further notes:
Report heart block if quality of single lead sufficient for accurate scoring
Ectopic beats reported if deemed clinically significant
Sustained sinus bradycardia or tachycardia defined by >30 s of stable rhythm, distinguished from transient responses associated with arousals or respiratory events
[a]Vagal tone higher in children and adolescents and therefore heart rate is lower during sleep compared to adults

Sleep Apnea and Atrial Fibrillation Pathophysiology

Multiple epidemiologic and clinic-based studies have pointed to the association of AF and OSA and nocturnal hypoxia which has paralleled experimental work underscoring specific underlying pathophysiological mechanisms. OSA is associated with autonomic nervous system imbalances. Hypoxia and hypercapnia associated with obstructive sleep apnea have been shown to cause autonomic nervous system imbalances in animal models. This can precipitate electrical changes and predispose the atria to arrhythmogenesis [19, 20]. Atrial remodeling can occur as a result of OSA. Negative intrathoracic pressure occurs as a result of forced inspiration against a closed airway. These forces may operate to increase atrial size and cardiac afterload, thus leading to atrial remodeling. Atrial remodeling has been linked to increased arrhythmia risk.

Elevation in inflammatory markers like C-reactive protein has been observed in patients with OSA [21]. Proinflammatory cytokines, such as interleukin-8 and cell adhesion molecules, are increased in patients with OSA, and decrease with CPAP therapy [22]. The percentage reduction of soluble IL-6 receptor levels and augmentation index was also improved in OSA patients treated with CPAP compared to sham CPAP in the Sleep Apnea Stress randomized trial [23]. Moreover, a hypercoagulable state has been observed in patients with OSA. Results from the Cleveland Family Study support an increase in plasminogen activator inhibitor-1 and fibrinogen level in response to exposure to even milder degrees of apnea [24]. These inflammatory effects on the coagulation system may increase risk for cardiac morbidity [22].

Some studies have suggested that OSA may directly lead to atrial fibrosis and accumulation of collagen deposition which can contribute to left atrial remodeling

[25]. The presence of OSA is associated with increase in expression of angiotensin-converting enzyme and concomitant decrease in synthesis of matrix metalloproteinase-2 [25]. Changes in electrical conduction could be another underlying mechanism increasing risk of arrhythmia in OSA.

CSA, identified to be associated with incident AF in epidemiologic studies, is defined as lack of drive to breathe during sleep, thus resulting in repetitive periods of insufficient ventilation and compromised gas exchange [26]. CSA is common in patients with stroke and congestive heart failure and also of higher prevalence in AF. CSA is also seen at high altitudes and in patients with OSA once PAP therapy is initiated [27]. In our patient, although there was a component of CSA at baseline, central events did not predominate; however treatment-emergent sleep apneas occurred. The pathophysiology of CSA is mediated by changes in arterial carbon dioxide pressure along with chronic hyperventilation. Prolonged circulation time also plays a role in its pathophysiology [28]. Manifestation of apnea is due to unstable ventilatory control. Controller gain (ventilator response to CO_2), plant gain (blood gas response to change in ventilation), and feedback gain (delay in feedback between the two imposed by hemoglobin binding and cardiac output) contribute to CSA [27]. In patients with high chemosensitivity, hyperventilation happens in response to mild increase in $PaCO_2$. This is followed by hypoventilation and possible apnea due to reduction of $PaCO_2$ below apneic threshold [27]. CSA is associated with fluctuations in CO_2 which along with arousals can increase sympathetic tone and cause structural and electrical remodeling [29]. Patients with CSA have been shown to have elevated levels of urinary and plasma epinephrine and norepinephrine [30]. CSA could also be marker of cardiac dysfunction or autonomic dysfunction that could in turn be linked to etiology of AF.

Once PAP therapy is started, emergence of central events secondary to PAP therapy poses a treatment challenge. These patients may need more than one titration study to find a pressure which provides adequate control of obstructive sleep apnea without inducing central apneas. Most of these patients will show improvement in central apnea burden after few months of treatment. Regular monitoring of AHI data from machine downloads is helpful.

Treatment of Obstructive Sleep Apnea in Atrial Fibrillation

Continuous positive airway pressure (CPAP) is the treatment of choice and is successful in 95% of patients when used consistently. Multiple trials have examined the effect of sleep apnea treatment with CPAP compared with either sham CPAP or another control on blood pressure outcomes. In a meta-analysis, CPAP was found to lead to an average systolic blood pressure reduction of about 2.5 mm Hg and a diastolic blood pressure reduction of 1.8 mm Hg [31, 32]. This is particularly meaningful as hypertension is a risk for AF. In a meta-analysis, use of CPAP was associated

with significant reduction in AF recurrence, and benefits of CPAP were stronger for younger, obese male patients [33].

In another meta-analysis, patients with untreated OSA were found to be at 57% greater risk of AF when compared to patients without OSA. In contrast, recurrence risks after cardioversion for AF for patients with CPAP treatment were similar to those without OSA [34]. Similar findings of a benefit of CPAP treatment for OSA translating into reduction of AF recurrence after ablation have been observed in several studies [35]. CPAP has also shown improvement in ventricular arrhythmias in heart failure patients [36]. Patients with frequent apneic episodes benefitted the most [37]. One of the challenges with CPAP use is limited adherence and tolerance. Approximately half of patients with AF and diagnosed OSA were found to be adherent to CPAP [38]. At times, due to challenges related to patient preference, claustrophobia, and especially adherence to PAP therapy, other options for management of OSA need to be considered.

Mandibular advancement device (MAD) or oral appliance therapy (OAT) may be effective in patients with mild obstructive sleep apnea. Meta-analyses of studies comparing OAT and CPAP have shown OAT to be non-inferior to CPAP therapy with regard to reduction in blood pressure [39]. Mandibular advancement device has been shown to be associated with significant drop of catalase activity and decrease in index of sleep autonomic variation compared with baseline levels [40]. Although not yet studied, this could conceivably translate into improvement in AF outcomes given that hypertension is a risk factor for AF, and increased inflammation can be involved in the pathophysiology of AF.

Hypoglossal nerve stimulator is a treatment option for CPAP-intolerant patients with moderate to severe obstructive sleep apnea. The therapy was approved by the US Food and Drug Administration in 2014. The therapy has most succes in patients with limited central events, and in those with anterior-posterior collapse of the airway (as oppose to concentric collapse) during a drug-induced sleep endoscopy [41]. A study focused on investigation of 12-month follow-up in patients on hypoglossal nerve stimulator therapy has shown that it appears to reduce heart rate variability during sleep [42].

Weight loss can contribute to improvement in OSA. A 10% weight loss has been shown to reduce AHI by 26%. Also, 10% weight gain has been linked to 32% increase in AHI [43]. Given that obesity increases risk of AF, weight reduction could be helpful in patients with OSA and AF.

Treatment of Central Sleep Apnea/Cheyne-Stokes Breathing in Atrial Fibrillation

Initial management approach to central sleep apnea/Cheyne-Stokes respiration (CSA/CSR) consists of medical management of underlying cardiac disorder. After this, continuous positive airway pressure is generally the next step in treatment. The Continuous Positive Airway Pressure Apnea Trial North American Program

(CAPNAP) trial was a multicenter trial which examined effects of CPAP on CSA outcomes in patients with heart failure. Use of CPAP showed 50% reduction in AHI and reduction in urinary catecholamines, but it did not show statistically significant difference in mortality when compared to the control group [44]. Supplemental oxygen is another treatment option for patients with heart failure and central sleep apnea. In a meta-analysis, nocturnal oxygen treatment was noted to be close to CPAP with regard to success in decreasing AHI in patients with CSA/CSR [45].

Phrenic nerve stimulation is a novel treatment approach for patients with CSA. It involves electric stimulation of phrenic nerve along with monitoring of patient's respiratory signals during sleep and results in integration of stimulated breaths with natural breathing. A multicenter, randomized controlled trial has shown that phrenic nerve stimulation may reduce central respiratory events frequency by about 50% [46]. The US Food and Drug Administration approved use of implanted phrenic nerve stimulator as treatment for moderate to severe central sleep apnea in 2017. Further investigation is needed to examine the impact of phrenic nerve stimulation on long-term cardiovascular outcomes and morbidity in AF.

Adaptive servo-ventilation (ASV) has previously shown efficacy in the reduction of AHI in patients with congestive heart failure and CSA/CSR; however per the results of Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure (SERVE-HF) trial, ASV confers an increase in mortality compared to medical management in patients with low left ventricular ejection fraction [47]. Factors which complicate interpretation of the study include insufficient data to understand the mechanistic or physiologic basis for these findings, in addition to a high percentage of crossover. Importantly, these results are not generalizable to patients treated with ASV for reasons other than heart failure-related CSA or to patients with heart failure with normal left ventricular ejection fraction [48, 49]. A small sub-study of the Cardiovascular Improvements with Minute Ventilation-Targeted ASV Therapy in Heart Failure (CAT-HF) trial identified a reduction in AF burden in response to ASV versus optimal medical therapy [50]. Future studies with larger sample sizes are needed to corroborate these findings.

Acetazolamide is a diuretic and also has respiratory stimulation properties. It is a carbonic anhydrase inhibitor and is thought to suppress CSA by widening delta CO_2 gap (i.e., increasing the apneic threshold). It may reduce AHI and improve daytime symptoms in patients with central sleep apnea and heart failure, although data specific to AF and respective outcomes are not available [51]. Adverse effects associated with acetazolamide limit its use. Theophylline use has shown to decrease AHI, primarily central apnea events, and duration of arterial oxyhemoglobin desaturation in stable heart failure patients [52]. However, its use is limited by its narrow safety range and multiple adverse effects. Rostral fluid shifts have been noted during sleep particularly in heart failure patients, thus contributing to both OSA and CSA. Pulmonary edema increases risk of CSA mediated via hyperventilation and subsequent hypocapnia. Treatment aimed at decreasing edema can help decrease risk of CSA-CSB in heart failure patients, and given the interplay of central sleep-disordered breathing and HF with AF, it is conceivable that these interventions may improve AF outcomes, albeit this has yet to be systematically studied [53].

Clinical Pearls

1. AF is the most prevalent sustained cardiac arrhythmia. Exact reasons for increase in AF incidence and prevalence are not known, but may be tied to increasing obesity in the population. There is a possibility that sleep apnea could be contributing in part to this trend.
2. Analysis from the Sleep Heart Health study suggests a temporal relationship between sleep-disordered breathing and arrhythmia. There was a higher risk of arrhythmia in the 90 seconds following a respiratory disturbance when compared to following normal breathing.
3. In several studies, use of CPAP was associated with significant reduction in AF recurrence.
4. Phrenic nerve stimulation is a novel treatment approach for patients with central sleep apnea. The US Food and Drug Administration approved use of implanted phrenic nerve stimulator as treatment for moderate to severe central sleep apnea in 2017.

References

1. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. Circulation. 2014;129:837–47.
2. Kim MH, Johnston SS, Chu B-C, Dalal MR, Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. Circ Cardiovasc Qual Outcomes. 2011;4:313–20.
3. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, et al. Lifetime risk for development of atrial fibrillation: the Framingham heart study. Circulation. 2004;110:1042–6.
4. Dilaveris PE, Kennedy HL. Silent atrial fibrillation: epidemiology, diagnosis, and clinical impact. Clin Cardiol. 2017;40:413–8.
5. Caldwell JC, Contractor H, Petkar S, Ali R, Clarke B, Garratt CJ, et al. Atrial fibrillation is under-recognized in chronic heart failure: insights from a heart failure cohort treated with cardiac resynchronization therapy. Europace. 2009;11:1295–300.
6. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, et al. Sleep apnea and cardiovascular disease. J Am Coll Cardiol. 2008;118:1080–111.
7. Kapur VK, Redline S, Nieto FJ, Young TB, Newman AB, Henderson JA. The relationship between chronically disrupted sleep and healthcare use. Sleep. 2002;25:289–96.
8. American Academy of Sleep Medicine. International classification of sleep disorders: diagnostic and coding manual. 3rd ed. Diagnostic Coding Manual; 2014.
9. Mehra R. Sleep apnea ABCs: airway, breathing, circulation. Cleve Clin J Med. 2014;81:479.
10. Wolk R, Kara T, Somers VK. Sleep-disordered breathing and cardiovascular disease. Circulation. 2003;108:9–12.
11. Gami AS, Caples SM, Somers VK. Obesity and obstructive sleep apnea. Endocrinol Metab Clin N Am. 2003;32:869–94.
12. Wanahita N, Messerli FH, Bangalore S, Gami AS, Somers VK, Steinberg JS. Atrial fibrillation and obesity-results of a meta-analysis. Am Heart J. 2008;155:310–5.
13. Gami AS, Hodge DO, Herges RM, Olson EJ, Nykodym J, Kara T, et al. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. J Am Coll Cardiol. 2007;49:565–71.

14. Holmqvist F, Guan N, Zhu Z, Kowey P, Allen L, Fonarow G, et al. Obstructive sleep apnea and atrial fibrillation: findings from orbit-AF. J Am Coll Cardiol. 2014;63:A292.
15. Mehra R, Benjamin EJ, Shahar E, Gottlieb DJ, Nawabit R, Kirchner HL, et al. Association of nocturnal arrhythmias with sleep-disordered breathing: the sleep heart health study. Am J Respir Crit Care Med. 2006;173(8):910–6.
16. Tung P, Levitzky YS, Wang R, Weng J, Quan SF, Gottlieb DJ, et al. Obstructive and central sleep apnea and the risk of incident atrial fibrillation in a community cohort of men and women. J Am Heart Assoc. 2017;6:e004500.
17. Monahan K, Storfer-Isser A, Mehra R, Shahar E, Mittleman M, Rottman J, et al. Triggering of nocturnal arrhythmias by sleep-disordered breathing events. J Am Coll Cardiol. 2009;54:1797–804.
18. Mehra R, Stone KL, Varosy PD, Hoffman AR, Marcus GM, Blackwell T, et al. Nocturnal arrhythmias across a spectrum of obstructive and central sleep-disordered breathing in older men: outcomes of sleep disorders in older men (MrOS sleep) study. Arch Intern Med. 2009;169:1147–55.
19. Lu Z, Nie L, He B, Yu L, Salim M, Huang B, et al. Increase in vulnerability of atrial fibrillation in an acute intermittent hypoxia model: importance of autonomic imbalance. Auton Neurosci. 2013;177:148–53.
20. Stevenson IH, Roberts-Thomson KC, Kistler PM, Edwards GA, Spence S, Sanders P, et al. Atrial electrophysiology is altered by acute hypercapnia but not hypoxemia: implications for promotion of atrial fibrillation in pulmonary disease and sleep apnea. Heart Rhythm. 2010;7:1263–70.
21. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. J Am Coll Cardiol. 2014;130:2071–104.
22. May AM, Mehra R. Obstructive sleep apnea: role of intermittent hypoxia and inflammation. Semin Respir Crit Care Med. 2014;35:531–44.
23. Paz y Mar HL, Hazen SL, Tracy RP, Strohl KP, Auckley D, Bena J, et al. Effect of continuous positive airway pressure on cardiovascular biomarkers: the sleep apnea stress randomized controlled trial. Chest. 2016;150:80–90.
24. Mehra R, Xu F, Babineau DC, Tracy RP, Jenny NS, Patel SR, et al. Sleep-disordered breathing and prothrombotic biomarkers: cross-sectional results of the Cleveland family study. Am J Respir Crit Care Med. 2010;182(6):826–33.
25. Ramos P, Rubies C, Torres M, Batlle M, Farre R, Brugada J, et al. Atrial fibrosis in a chronic murine model of obstructive sleep apnea: mechanisms and prevention by mesenchymal stem cells. Respir Res. 2014;15:54.
26. Eckert DJ, Jordan AS, Merchia P, Malhotra A. Central sleep apnea: pathophysiology and treatment. Chest. 2007;131:595–607.
27. Leung RST, Comondore VR, Ryan CM, Stevens D. Mechanisms of sleep-disordered breathing: causes and consequences. Pflugers Arch. 2012;463:213–30.
28. Flinta I, Ponikowski P. Relationship between central sleep apnea and Cheyne−stokes respiration. Int J Cardiol. 2016;206:S8–12.
29. Sin DD, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. Am J Respir Crit Care Med. 1999;160:1101–6.
30. Naughton MT, Benard DC, Liu PP, Rutherford R, Rankin F, Bradley TD. Effects of nasal CPAP on sympathetic activity in patients with heart failure and central sleep apnea. Am J Respir Crit Care Med. 1995;152:473–9.
31. Bazzano LA, Khan Z, Reynolds K, He J. Effect of nocturnal nasal continuous positive airway pressure on blood pressure in obstructive sleep apnea. Hypertension. 2007;50:417–23.
32. Logan AG, Perlikowski SM, Mente A, Tisler A, Tkacova R, Niroumand M, et al. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. J Hypertens. 2001;19:2271–7.
33. Qureshi WT, bin Nasir U, Alqalyoobi S, O'Neal WT, Mawri S, Sabbagh S, et al. Meta-analysis of continuous positive airway pressure as a therapy of atrial fibrillation in obstructive sleep apnea. Am J Cardiol. 2015;116:1767–73.

34. Li L, Wang Z-W, Li J, Ge X, Guo L-Z, Wang Y, et al. Efficacy of catheter ablation of atrial fibrillation in patients with obstructive sleep apnoea with and without continuous positive airway pressure treatment: a meta-analysis of observational studies. Europace. 2014;16:1309–14.
35. Fein AS, Shvilkin A, Shah D, Haffajee CI, Das S, Kumar K, et al. Treatment of obstructive sleep apnea reduces the risk of atrial fibrillation recurrence after catheter ablation. J Am Coll Cardiol. 2013;62:300–5.
36. Ryan CM, Usui K, Floras JS, Bradley TD. Effect of continuous positive airway pressure on ventricular ectopy in heart failure patients with obstructive sleep apnoea. Thorax. 2005;60:781–5.
37. Fava C, Dorigoni S, Dalle Vedove F, Danese E, Montagnana M, Guidi GC, et al. Effect of CPAP on blood pressure in patients with OSA/hypopnea: a systematic review and meta-analysis. Chest. 2014;145:762–71.
38. Patel D, Mohanty P, Di Biase L, Shaheen M, Lewis WR, Quan K, et al. Safety and efficacy of pulmonary vein antral isolation in patients with obstructive sleep apnea: the impact of continuous positive airway pressure. Circulation. 2010;3:445–51.
39. de Vries GE, Wijkstra PJ, Houwerzijl EJ, Kerstjens HAM, Hoekema A. Cardiovascular effects of oral appliance therapy in obstructive sleep apnea: a systematic review and meta-analysis. Sleep Med Rev. 2018;40:55–68.
40. Dal-Fabbro C, Garbuio S, D'Almeida V, Cintra FD, Tufik S, Bittencourt L. Mandibular advancement device and CPAP upon cardiovascular parameters in OSA. Sleep Breath. 2014;18:749–59.
41. Strohl MM, Yamauchi M, Peng Z, Strohl KP. Insights since FDA approval of hypoglossal nerve stimulation for the treatment of obstructive sleep apnea. Curr Sleep Med Rep. 2017;3:133–41.
42. Dedhia R, Bliwise D, Quyyumi A, Strollo P, Li Q, Clifford G. Impact of hypogloassal nerve stimulation on heart rate variability: the star trial. Sleep. 2017;40:A210.
43. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. J Am Med Assoc. 2000;284:3015–21.
44. Bradley TD, Logan AG, Kimoff RJ, Sériès F, Morrison D, Ferguson K, et al. Continuous positive airway pressure for central sleep apnea and heart failure. N Engl J Med. 2005;353:2025–33.
45. Bordier P, Lataste A, Hofmann P, Robert F, Bourenane G. Nocturnal oxygen therapy in patients with chronic heart failure and sleep apnea: a systematic review. Sleep Med. 2016;17:149–57.
46. Costanzo MR, Ponikowski P, Javaheri S, Augostini R, Goldberg L, Holcomb R, et al. Transvenous neurostimulation for central sleep apnoea: a randomised controlled trial. Lancet. 2016;388:974–82.
47. Cowie MR, Woehrle H, Wegscheider K, Angermann C, d'Ortho M-P, Erdmann E, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. N Engl J Med. 2015;373:1095–105.
48. Aurora RN, Bista SR, Casey KR, Chowdhuri S, Kristo DA, Mallea JM, et al. Updated adaptive servo-ventilation recommendations for the 2012 AASM guideline: "the treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses.". J Clin Sleep Med. 2016;12:757–61.
49. Mehra R, Gottlieb DJ. A paradigm shift in the treatment of central sleep apnea in heart failure. Chest. 2015;148:848–51.
50. Piccini JP, Pokorney SD, Anstrom KJ, Oldenburg O, Punjabi NM, Fiuzat M, et al. Adaptive servo-ventilation reduces atrial fibrillation burden in patients with heart failure and sleep apnea. Heart Rhythm [Internet]. 2018;(August):1–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1547527118307197
51. Javaheri S. Acetazolamide improves central sleep apnea in heart failure: a double-blind, prospective study. Am J Respir Crit Care Med. 2006;173:234–7.
52. Javaheri S, Parker TJ, Wexler L, Liming JD, Lindower P, Roselle GA. Effect of theophylline on sleep-disordered breathing in heart failure. N Engl J Med. 1996;335:562–7.
53. White LH, Bradley TD. Role of nocturnal rostral fluid shift in the pathogenesis of obstructive and central sleep apnoea. J Physiol. 2013;591:1179–93.
54. Caples SM, Rosen CL, Shen WK, Gami AS, Cotts W, Adams M, et al. The scoring of cardiac events during sleep. J Clin Sleep Med. 2007;3(2):147–54.

Chapter 5
Cheyne-Stokes Breathing and Diastolic Heart Failure

J. Verbraecken and S. Javaheri

Case

A 74-year-old Caucasian male (Fig. 5.1), non-smoker, usually drinking five cups of coffee per day, was referred to our sleep clinic because of mild chronic insomnia which started approximately 5 years ago. The patient was affected by stable diastolic heart failure due to atrial fibrillation and arterial hypertension. Two years before, a single-chamber rate-responsive pacemaker was implanted. He had been suffering from progressive intermittent snoring, fatigue, and mild sleepiness for years. Witnessed apneas were also reported. He complained of fragmented, unrefreshing sleep despite averaging 8.5 h of sleep per night. He also awoke to use the bathroom once a night. There was no suspicion of depression. No restless legs symptoms or periodic leg movements were reported. He did not use alcohol on a regular base. Physical examination revealed obesity (BMI of 30.5 kg/m^2, neck circumference 47 cm, waist circumference 107 cm, hip circumference 109 cm, fat ratio 29.2%) and elevated blood pressure (systolic blood pressure of 158 mmHg, diastolic blood pressure 97 mmHg). Epworth sleepiness score was 10/24, and the New York Heart Association (NYHA) class was 1. Arterial blood gas analysis was performed with the following values: pH of 7.46, $PaCO_2$ 32.1 mmHg, PaO_2 95.9 mmHg, and SaO_2 98.2%. NT-proBNP was elevated (743 pg/mL). Lung function measurements revealed an FEV1 of 4.25 L (147% of the predicted value), a Tiffeneau index of 69, and a TLC of 8.53 L (121% predicted). Diffusion capacity

J. Verbraecken (✉)
Department of Pulmonary Medicine and Multidisciplinary Sleep Disorders Centre, Antwerp University Hospital and University of Antwerp, Antwerp, Belgium
e-mail: johan.verbraecken@uza.be

S. Javaheri
Bethesda North Hospital, Cincinnati, OH, USA

C. Won (ed.), *Complex Sleep Breathing Disorders*,
https://doi.org/10.1007/978-3-030-57942-5_5

was 108% predicted. He was taking oral anticoagulant therapy, simvastatin (20 mg/day), perindopril 10 mg, and indapamide 1.25 mg a day. Echocardiography showed mild concentric left ventricular hypertrophy, a left ventricular ejection fraction (LVEF) of 50% (2D-Simpson), moderate bi-atrial and bi-ventricular dilatation, and mild elevated end-diastolic LV pressure (see Table 5.1). Polysomnography was

Fig. 5.1 De-identified photograph of the case described

Table 5.1 Echocardiographic parameters before and after ASV therapy

	At diagnosis	After 1 year of ASV	Normal value
Mean PAP (mmHg)	36	30	10–20
Left atrial diameter (mm)	51	62.8	30–40
Left atrial volume (mm)	167	130	18–58
LAVI (mL/m^2)	77.54	61.22	30–38
EE'	12.8	12	<10
LVEF (Simpson, %)	50	57	>55%
LVIDd (mm)	64	58.4	42–59
IVS (mm)	14.95	13.5	6–12
LVPWd (mm)	12	11.2	6–12

Legend: *PAP* Pulmonary arterial pressure, *LVEF* left ventricular ejection fraction, *LAVI* left atrial volume index, *EE'* the ratio between early mitral inflow velocity and mitral annular early diastolic velocity, *LVIDd* left ventricular internal dimension during diastole, *IVS* interventricular septum thickness, *LVPWd* left ventricular posterior wall dimension

performed, scoring sleep stages according to the American Academy of Sleep Medicine (AASM) 2007 criteria [1] and breathing according to AASM 2012 criteria [2].

Baseline Night

The baseline recording (Figs. 5.2 and 5.3 and Table 5.2) showed a series of central apneas (central apnea-hypopnea index (AHI) = 31/h), associated with significant fluctuations in peripheral oxygen saturation (oxygen desaturation index (ODI) = 19.1/h) in a context of Cheyne-Stokes breathing (CSB) pattern. Breathing events were prevalent in NREM sleep (AHI-NREM = 32.6/h), especially during sleep stages N1 and N2 and were less frequent in slow-wave sleep and REM sleep (AHI-REM = 21.2/h). The oxygen saturation values did not drop below 90%. Snoring was rare and few obstructive events were detected. Two short periods of periodic leg movements were recorded. Sleep architecture was disrupted, with

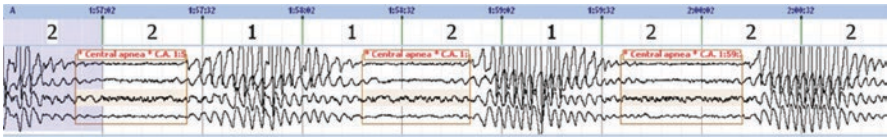


Fig. 5.2 Characteristic central sleep apneas with a crescendo-decrescendo flow pattern (Cheyne-Stokes breathing)

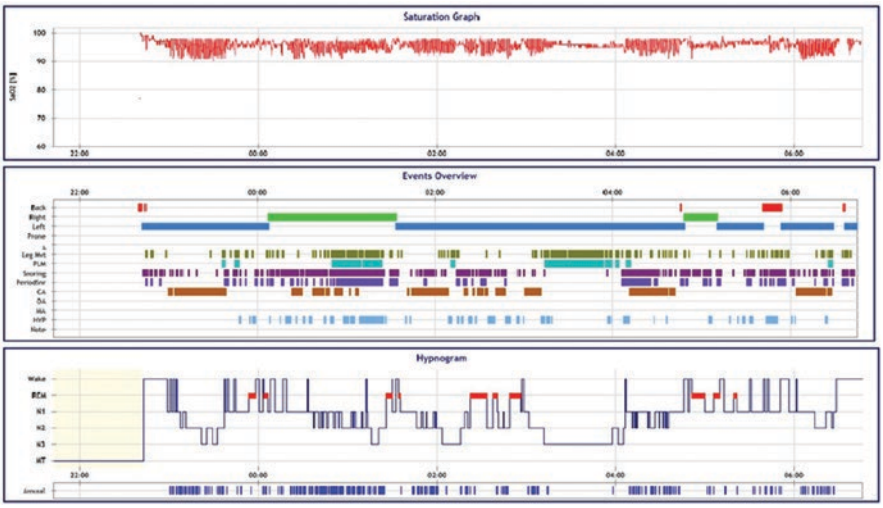


Fig. 5.3 Polysomnographic trend of the diagnostic night. Note very few central events occur during REM and N3 sleep.

Table 5.2 Polysomnographic parameters at diagnosis, during CPAP titration, and after ASV therapy

	Diagnosis	CPAP titration	ASV (2 M)	ASV (1 Y)
TST (min)	413	302	348	297
SEI (TST/TIB, %)	85.6	63.0	71.9	60.3
SL (min)	16.6	17.1	16.7	14.4
WASO (min)	36	148	85	181
NREM (%)	87.7	89.9	80.5	80.6
SWS (%)	17.7	7.3	15.7	9.6
REM (%)	12.3	10.1	19.5	19.4
AHI (#/h)	31.2	40.1	0	0.4
AHI-NREM (#/h)	32.6	42.8	0	0.0
AHI-REM (#/h)	21.2	15.7	0	2.1
OAI (#/h)	0	0	0	0
CAI (#/h)	31.2	0	0	0
HI (#/h)	12.3	40.1	0	0.4
Apnea duration (s)	31.6	0	0	0
Hypopnea duration (s)	24.8	29.5	0	33.0
Mean SaO_2 (%)	95.7	96.5	96.9	96.8
Min SaO_2 (%)	77	91	90	95
$SaO_2 < 90\%$ (min)	0	0	0	0
ODI (#/h)	19.1	40.1	1.6	0.6

TST Total sleep time in min, *SEI* sleep efficiency index in %, *SL* sleep latency time in min, *NREM* non-rapid eye movement sleep in %TST, *REM* rapid eye movement sleep in %TST, *AHI* apnea-hypopnea index, *AHI-NREM* AHI during NREM sleep, *AHI-REM* AHI during REM sleep, *OAI* obstructive apnea index, *CAI* central apnea index, *HI* hypopnea index, *ODI* oxygen desaturation index (#/h)

modest reduction in sleep efficiency, total sleep time, and percentage of slow-wave (17.7%) and REM sleep. Sleep latency was normal, while wake time after sleep onset (WASO) was longer than 30 min.

CPAP Titration Night

During the second night (Fig. 5.4 and Table 5.2), continuous positive airway pressure (CPAP) therapy was titrated from 5 to 15 cmH_2O. A full face mask was applied. There were persistent central apneas (AHI 40.0/h), again with features of CSB. The lowest oxygen saturation was 91%. Sleep efficiency, total sleep time, and percentage of slow wave (7.3%) and REM (10.1%) sleep were worse. Sleep latency was within normal limits, while WASO was 148 min.

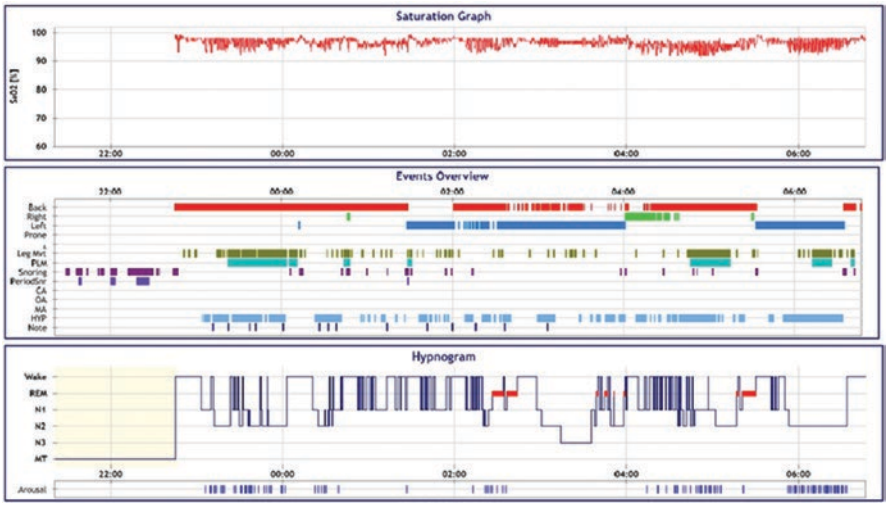


Fig. 5.4 Polysomnographic trend of the CPAP titration night

ASV Control Nights

Finally, the patient was prescribed adaptive servo-ventilation (ASV) which was set as follows: ASV, auto; expiratory positive airway pressure (EPAP), 4–8 cmH_2O, and pressure support (PS) range, 4–10 cmH_2O. A polysomnographic recording with ASV 2 months later showed improvement in respiratory events (Fig. 5.5 and Table 5.2). Breathing events were absent and the oxygen saturation remained greater than 90%. Sleep architecture was still disrupted but with an increased percentage of slow wave (15.7%) and REM sleep (19.5%). Sleep latency was still normal, while WASO improved to 85 min. After 1-year follow-up, a polysomnography confirmed the efficacy of nocturnal ventilation in controlling breathing events, while sleep quality was still not optimal (Fig. 5.6 and Table 5.2).

Chronic Follow-Up with ASV

Although the problem of maintaining sleep persisted, our patient perceived considerable improvement in sleep quality. Since the start of ASV, a progressive improvement could be observed, with more alertness and less dyspnea. Moreover, the fatigue, hypersomnia, nocturia, and restlessness during sleep—the patient's most important complaints—disappeared. Caffeine intake was lowered to two cups of coffee a day. His quality of life improved considerably, and he also experienced less discomfort when performing moderate exercise. His BMI decreased to 28.9 kg/m^2, while the Epworth sleepiness score improved to 0–5/24. The NYHA class remained

Fig. 5.5 Polysomnographic trend after 2 months of ASV therapy

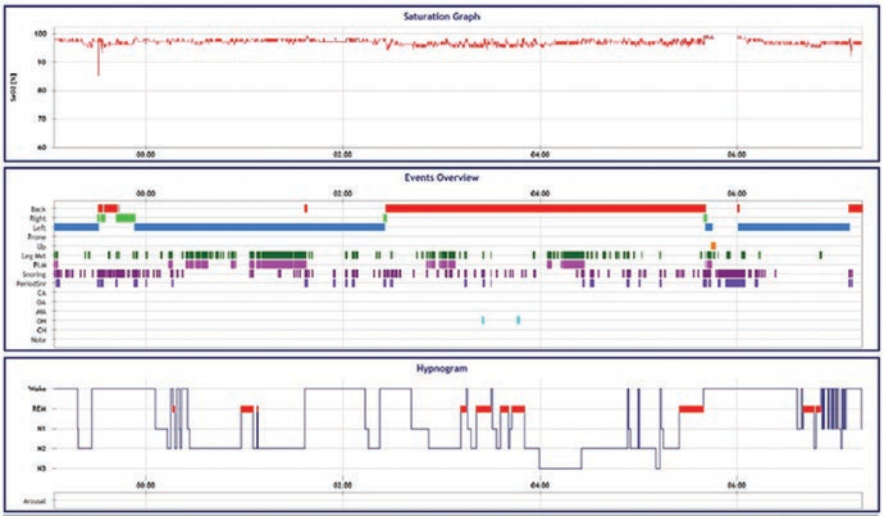


Fig. 5.6 Polysomnographic trend after 1 year of ASV therapy

1. Blood pressures decreased to 128 mmHg (systolic) and 82 mmHg (diastolic) after 2 months and to 124 mmHg (systolic) and 77 mmHg (diastolic) after 1 year on ASV therapy. LVEF substantially improved by 7%, but relative improvement was 15%. Pulmonary artery pressures also improved after chronic ASV treatment, though the NT-proBNP remained high (838 pg/mL). The treatment with ASV was generally well accepted and tolerated. He used his ASV device 7.7 h per night (approximately 90.6% of time in bed), with absence of significant leakage (2.1 L/min). In order to solve the residual insomnia problem, cognitive behavioral therapy was initiated.

Discussion

The case described in this paper is a typical presentation of CSB in association with diastolic heart failure due to atrial fibrillation and moderately severe insomnia. CSB is typically characterized by recurrent central apneas or hypopneas alternating with a ventilatory phase, presenting as a crescendo-decrescendo pattern of flow. A cycle length of >40 s and a "waxing and waning" pattern of ventilation typically distinguish CSB from other central sleep apnea (CSA) types. The majority of patients with CSB have either systolic or diastolic congestive heart failure (CHF). In 2017, the European Respiratory Society (ERS) Task Force on central sleep apnea recommended replacing the historical term "Cheyne-Stokes respiration" by "periodic breathing in heart failure" or "chronic heart failure with central sleep apnea/periodic breathing (CSA/PB)" [3]. In this chapter, we will use the terms interchangeably. CSB can also manifest following stroke or may be associated with other neurological disorders; very rarely do idiopathic cases occur. Patients with CSB usually are normocapnic or hypocapnic. According to the International Classification of Sleep Disorders – Third Edition (ICSD-3) diagnostic criteria for CSB, either symptoms or a comorbid condition must be present [4]. If neither symptoms nor comorbid conditions are present, CSB is less relevant and considered a polysomnographic finding. More than 50% of respiratory events must be of central origin and meet the criteria for CSB. Particular features can help to distinguish CSB from idiopathic CSA and can give insight in the underlying pathology. In patients with CSB, arousal from sleep tends to occur at the zenith of respiratory effort, between episodes of apneas and hypopneas, rather than at apnea termination. Overall, these patients have a longer cycle length compared to those in primary CSA, caused by a long ventilatory period. Also, the nadir of the oxygen saturation is in the middle of the apnea, which is explained by an increased circulation time as seen with decreased cardiac output. CHF with CSA/PB occurs most commonly in patients with left ventricular systolic heart failure but may also present in patients with diastolic dysfunction. In case of diastolic CHF, the cycle length of CSA/PB is shorter compared to systolic CHF, as the ejection fraction is normal. On the other hand, the worse the systolic function, the longer is the cycle length (given the longer ventilatory period between respiratory events).

Our case was known with an established diagnosis of diastolic heart failure. Heart failure is a complex clinical syndrome that results from a structural or functional impairment of contraction or filling of the heart, resulting in the inability to meet the metabolic needs of the body. Diastolic dysfunction refers to an abnormality of diastolic distensibility, filling, or relaxation of the left ventricle. If effort intolerance and dyspnea develop in such a patients, it is appropriate to use the term "diastolic heart failure." Current classification of heart failure is based on the LVEF [5]. Most recent guidelines separate heart failure with reduced ejection fraction (<40%, HFrEF) from midrange (40–49%) and preserved ejection fraction (≥50%, HFpEF) [5]. The diagnosis of HFpEF is more challenging than the diagnosis of HFrEF. On the one hand, patients with HFpEF generally do not present with a dilated left ventricle, but have increased wall thickness, increased left atrial size,

and signs of increased filling pressures. In short, impaired left ventricular filling capacity is a likely cause of heart failure in these patients (diastolic heart failure). On the other hand, HFrEF presents with dilatation of the left ventricle. These patients are characterized by symptoms of breathlessness, peripheral edema, and fatigue due to pulmonary congestions and reduced output. To make it even more complex, most patients with HFrEF also have diastolic dysfunction, while subtle abnormalities of systolic function may be present in patients with HFpEF. The prevalence of CHF is approximately 1–2% of the adult population in developed countries, rising to >10% among people >70 years of age. The proportion of patients with HFpEF ranges from 22% to 73%. Compared to HFrEF, patients with HFpEF are older and more often women and more commonly have a history of arterial hypertension and atrial fibrillation, while a history of myocardial infarction is less common. These epidemic proportions, together with the few effective treatments, make HFpEF one of the greatest unmet needs in the current field of cardiology [6]. Prognosis is equally grim in HFrEF: 5-year mortality is around 75%, which is worse than most cancers. The plasma concentration of natriuretic peptides (NP) can be used as an initial diagnostic test, especially in the non-acute setting. Plasma concentrations of BNP < 35 pg/mL and/or NT-proBNP <125 pg/mL make a diagnosis of HFpEF or HFrEF unlikely. NT-proBNP was obviously elevated in our case. Notably, the diagnosis of HFpEF in patients with atrial fibrillation is difficult, since atrial fibrillation itself is associated with higher NP levels. In such setting, higher cut-offs have to be used [5].

CSA/PB is most commonly seen in patients with HFrEF – up to 50% of these patients may have such a breathing pattern. However, the prevalence of CSA/PB in HFpEF, as in our case, is less well defined. Estimates vary between 18% and 30% depending on body weight, the different diagnostic criteria of HFpEF, and the cut-off levels used [7–10]. Prevalence of CSA/PB increases with increasing impairment of diastolic function [7]. Presence of cardiovascular comorbidities can contribute to the severity of heart failure—such as arterial hypertension, coronary artery disease, myocardial ischemia, and atrial fibrillation—and may worsen CSA/PB [11]. Patients with hypertension, such as in the present case, and particularly those with left ventricular hypertrophy, are susceptible to diastolic heart failure. They are unable to increase their end-diastolic volume, because of decreased left ventricular relaxation and compliance. Consequently, this provokes a cascade, in which the left ventricular end-diastolic pressure rises, left atrial pressure increases, and pulmonary edema develops. Evidence that CSA/PB aggravates hypertension, coronary artery disease, or atrial fibrillation is sparse. However, treatment as in our case can result in an improved blood pressure profile, suggesting a direct relationship.

Patients with CSA/PB may complain of typical symptoms of sleep apnea, including daytime sleepiness or disturbed sleep. However, the majority of the patients do not complain of excessive daytime sleepiness. Despite the lack of symptoms in CSA/PB, improvement in sleep quality and objective daytime sleepiness with successful treatment has been described. While it is recognized that CHF contributes to the development of CSA [12] and that CSA is associated with worse prognosis in these patients, the role of treatment of CSA in CHF is of debate. The recent ERS

statement paper by Randerath et al. and the extensive systematic review by Aurora et al. contain many relevant references for treatment of CSA/PB [3, 13]. The first intervention in patients with CSA/PB is always to optimize treatment for the underlying CHF. For this, diuretics can be used to reduce pulmonary congestion and cardiac filling pressures, beta-blockers to diminish excessive sympathetic activation, and angiotensin-converting enzyme inhibitors to reduce ventricular afterload. In HFpEF, the evidence that diuretics improve symptoms is similar across the spectrum of LVEF. For other drug categories, the evidence is lacking or inconsistent. Circumstantial evidence suggests that treating hypertension, often predominantly systolic, is important in HFpEF. The blood pressure targets recommended in hypertension guidelines are applicable to CHF [5]. Physical activity, salt restriction, and compression stockings can also reduce fluid retention and accumulation in the lower limbs during daytime and diminish nocturnal fluid shift to lungs and upper airways [14]. Optimal cardiac failure treatment also includes a surgical approach on cardiac vessels or valves. Atrial overdrive pacing at a rate 15 beats faster than the mean nocturnal heart rate has also been shown to improve CSA/PB. Resynchronization therapy has been shown to decrease respiratory instability and improve cardiac function, quality of life, and mortality in more advanced disease.

Pharmacological treatment of CSA/PB with respiratory stimulants has been tried, including theophylline, acetazolamide, as well as with hypnotics, but its overall impact is weak, and, hence, not widely used [15, 16].

The Canadian Positive Airway Pressure Trial for Heart Failure Patients with Central Sleep Apnea (CANPAP) trial provided evidence that about 50% of patients will respond to CPAP, with a reduction in the frequency of episodes of apnea and hypopnea, an improvement of LVEF, and 6-min walk test distance, but without improved prognosis or rate of heart failure-related hospitalizations. This warrants a trial with CPAP; in our case, however, CPAP was not unsuccessful [17, 18]. CANPAP emphasized that an improved survival may only manifest in patients whose AHI is reduced to <15/h [17]. The mechanisms of action of CPAP include decreasing venous return and unloading the left ventricle, thereby decreasing pulmonary capillary wedge pressure and increasing functional residual capacity. Moreover, in some patients with CSA, upper airway collapse occurs which is reversed by CPAP.

If CSA/PB does not respond to CPAP, ASV will usually be effective. ASV machines track minute ventilation or peak flow and adjust pressure support to stabilize ventilation or the mean amplitude of peak airflow during breathing. In our patient, CPAP was not effective for central respiratory events, but a subsequent titration with ASV reduced the AHI to 0/hr. An ASV device download after 2 months and 1 year of treatment showed an AHI close to 0/hr., and the patient felt much improved on ASV. However, we have to bear in mind that the majority of the evidence on CSA treatment with ASV in CHF is based on studies in systolic heart failure—with evidence suggesting an increased mortality in ASV users with LVEF <45%. Few data are available on treatment of CSA/PB in HFpEF (or HFrEF with concomitant diastolic dysfunction) [18–20]. In one observational, uncontrolled study [21], ASV reduced CSA/PB and improved cardiac function in diastolic heart failure. Our case is in line with these findings, demonstrating improved blood pressure profile and hemodynamic

changes. Another study addressed the potential prognostic impact of sleep-disordered breathing in 36 patients with HFpEF: ASV significantly improved the central as well as the obstructive apnea index, with an 18-month higher event-free rate [19].

However, this enthusiasm has to be tempered, when looking to the number of patients effectively achieving success, which was only 70% in a real-life study that included central sleep apnea of different etiologies [22, 23]. Moreover, ¼ of them refused to start the treatment at home. After 5 months of therapy, 84% of the patients were still using ASV, with only 50% of them reporting "much improvement" in sleep quality and 36% reporting "much improvement" in daytime sleepiness, based on a subjective survey by telephone contact. This reflects the masking of the typical symptoms of sleep apnea by the symptoms of their underlying heart disease and by an increased sympathetic activity. The heterogeneous and contradictory results on ASV ask for more accurate patient's phenomapping. Apart from the AHI and LVEF, a number of pathophysiologic traits underlying CSA/PB patterns during sleep have been suggested, including the burden of hypoxemia, the variations of oxygen desaturation, the chemoresponsiveness, the ventilatory instability during wakefulness and sleep, and the end-expiratory lung volume. The advantages of ASV have also to be weighed versus the substantial costs of ASV devices, and despite its superiority, ASV has to be prescribed in a stepwise approach. Some guidance was given by Momura S et al., who recommended ASV in those with persisting respiratory events (>15/h) during a CPAP titration night [24]. On the other hand, therapy should be considered at the earliest moment in the course when clinical symptoms (and cardiovascular burden of the disease) might be minimal [25]. The current priority is to search for phenotypes of CHF patients that may benefit most from treatment guiding individualized and personalized management.

Our case suffered from concomitant moderately severe insomnia. The prevalence of insomnia symptoms among patients with CHF is high, ranging from 23% to 73%, including difficulty maintaining sleep (34–43%), falling asleep (23–47%), and waking too early in the morning (35–39%) [26]. CHF patients are also consistently more likely to have objective findings of prolonged sleep latency and poor sleep continuity. The reasons are multifactorial. In addition to sleep-disordered breathing such as CSA/PB, symptoms of CHF itself such as orthopnea, paroxysmal nocturnal dyspnea, coughing, and nocturia often lead to insomnia, and insomnia itself may reflect the severity of CHF. Moreover, insomnia may also be an indicator of depression, which is associated with adverse prognosis of CHF. Insomnia could also be partially caused by medications used in the treatment of CHF. For example, beta-blockers may affect production of melatonin, and diuretics may cause nocturia, which all together could result in poor sleep quality. Patients with CHF who also have insomnia develop fatigue and worsening physical performance, and these symptoms are associated with decreased quality of life and low medication adherence. CHF patients with insomnia also have a significantly higher rate of cardiac events. The hyperarousal disorder is accompanied by chronic activation of stress responses with increased activity in the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, leading to an increased secretion of cortisol and upregulation of the renin-angiotensin-aldosterone system (RAAS). Stress response

caused by insomnia is also accompanied by increased blood pressure, increased heart rate, decreased heart rate variability, secretion of catecholamines and pro-inflammatory cytokines, and impaired exercise capacity and activity, which are risk factors for the progression of CHF and prognostic factors of CHF. Thus, treatment of insomnia might improve both quality of life and overall prognosis.

In our patient, problems with maintaining sleep persisted after initiation of ASV therapy, and thus cognitive behavioral therapy was proposed, with the addition of strict sleep hygiene rules, such as minimal use of caffeine, maintaining a regular sleep schedule, going to bed only when sleepy, regular exercise, and only short naps. Such approach can lead to improvement in insomnia in 58% of the cases, and 25% can achieve remission of insomnia symptoms, along with improvement in depression and anxiety.

Key Learning Points

- CPAP and supplemental oxygen are often effective at reducing the AHI in CSA/PB associated with heart failure. These are generally considered first-line therapies, although outcomes studies have yet to show long-term benefit.
- ASV is an effective treatment modality for CSA/PB, and a valuable complement to the management of heart failure. However, ASV therapy has been associated with increased mortality in those with reduced left ventricular ejection fraction. Its long-term benefits or risks in diastolic dysfunction or heart failure with preserved EF remain unknown.
- ASV includes ventilatory support with variable synchronization dependent on flow and ventilation. This type of ventilation is anti-cyclic to the periodicity of the patient's own breathing and acts to dampen the oscillations in the ventilatory drive that underlie periodic breathing. A common feature in treating patients with CSA/PB is that only some patients respond.
- Patients whose CSA does not resolve with treatment are those with the most unstable respiratory control (or the highest loop gain). Uncontrollable CSA may be an indicator of a worse prognosis in CHF.
- Insomnia is highly prevalent in CHF. Insomnia contributes to fatigue and poor quality of life, as well as may be associated with adverse outcomes in CHF patients. CHF disease management alone may not be sufficient to ameliorate insomnia symptoms. Understanding the nature of insomnia symptoms and their associations with daytime symptoms and functional performance is necessary to guide sleep disorders treatment for CHF patients. Identification of CHF patients who may benefit from pharmacological and/or behavioral insomnia treatment is needed.

References

1. Iber C, Ancoli-Israel S, Chesson AL Jr., Quan SF; for the American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. 1st ed. Westchester: American Academy of Sleep Medicine; 2007.
2. Berry RB, Budhiraja R, Gottlieb DJ; American Academy of Sleep Medicine, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. Deliberations of the sleep apnea definitions task force of the American Academy of Sleep Medicine. J Clin Sleep Med. 2012;8(5):597–619.
3. Randerath W, Verbraecken J, Andreas S, et al. Definition, discrimination, diagnosis and treatment of central breathing disturbances during sleep. Eur Respir J. 2017;49(1). pii: 1600959.
4. International classification of sleep disorders. 3rd ed. Darien: AASM.
5. Ponikowski P, Voors AA, Anker SD; ESC Scientific Document Group, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129–200.
6. Gevaert AB, Boen JRA, Segers VF, Van Craenenbroeck EM. Heart failure with preserved ejection fraction: a review of cardiac and noncardiac pathophysiology. Front Physiol. 2019;10:638.
7. Bitter T, Faber L, Hering D, et al. Sleep-disordered breathing in heart failure with normal left ventricular ejection fraction. Eur J Heart Fail. 2009;11:602–8.
8. Chan J, Sanderson J, Chan W, et al. Prevalence of sleep-disordered breathing in diastolic heart failure. Chest. 1997;111:1488–93.
9. Sekizuka H, Osada N, Miyake F. Sleep disordered breathing in heart failure patients with reduced versus preserved ejection fraction. Heart Lung Circ. 2013;22:104–9.
10. Shah RV, Abbasi SA, Heydari B, et al. Obesity and sleep apnea are independently associated with adverse left ventricular remodeling and clinical outcome in patients with atrial fibrillation and preserved ventricular function. Am Heart J. 2014;167:620–6.
11. Oldenburg O, Bitter T, Fox H, et al. Heart failure. Somnology. 2014;18:19–25.
12. Mansfield DR, Solin P, Roebuck T, et al. The effect of successful heart transplant treatment of heart failure on central sleep apnea. Chest. 2003;124:1675–81.
13. Aurora RN, Chowdhuri S, Ramar K, et al. The treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses. Sleep. 2012;35:17–40.
14. Perger E, Jutant EM, Redolfi S. Targeting volume overload and overnight rostral fluid shift: a new perspective to treat sleep apnea. Sleep Med Rev. 2018;42:160–70.
15. Javaheri S, Parker TJ, Wexler L, Liming JD, Lindower P, Roselle GA. Effect of theophylline on sleep-disordered breathing in heart failure. N Engl J Med. 1996;335(8):562–7.
16. Javaheri S. Acetazolamide improves central sleep apnea in heart failure: a double-blind, prospective study. Am J Respir Crit Care Med. 2006;173(2):234–7.
17. Arzt M, Floras JS, Logan AG, Kimoff RJ, Series F, Morrison D, et al. Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP). Circulation. 2007;115(25):3173–80.
18. Hetland A, Haugaa KH, Olseng M, et al. Three-month treatment with adaptive servoventilation improves cardiac function and physical activity in patients with chronic heart failure and Cheyne–Stokes respiration: a prospective randomized controlled trial. Cardiology. 2013;126:81–90.
19. Yoshihisa A, Suzuki S, Yamaki T, et al. Impact of adaptive servo-ventilation on cardiovascular function and prognosis in heart failure patients with preserved left ventricular ejection fraction and sleep-disordered breathing. Eur J Heart Fail. 2013;15:543–50.

20. Birner C, Series F, Lewis K, et al. Effects of auto-servo ventilation on patients with sleep-disordered breathing, stable systolic heart failure and concomitant diastolic dysfunction: sub-analysis of a randomized controlled trial. Respiration. 2014;87:54–62.
21. Bitter T, Westerheide N, Faber L, et al. Adaptive servoventilation in diastolic heart failure and Cheyne–Stokes respiration. Eur Respir J. 2010;36:385–92.
22. Allam JS, Olson EJ, Gay PC, Morgenthaler TI. Efficacy of adaptive servoventilation in treatment of complex and central sleep apnea syndromes. Chest. 2007;132:1839–46.
23. Verbraecken J. From CPAP to trilevel adaptive servo ventilation in chronic heart failure--have we got the magic bullet? Sleep Med. 2014;15(8):846–8.
24. Momura S. Treatment of Cheyne-Stokes respiration-central sleep apnea in patients with heart failure. J Cardiol. 2012;59(2):110–6.
25. Javaheri S, Susan R. Insomnia and Risk of Cardiovascular Disease. Chest. 2017;152(2):435–44.
26. Redeker NS, Jeon S, Muench U, Campbell D, Walsleben J, Rapoport DM. Insomnia symptoms and daytime function in stable heart failure. Sleep. 2010;33(9):1210–6.

Chapter 6
Pulmonary Hypertension in Obstructive Sleep Apnea

Vahid Mohsenin

Introduction

Pulmonary hypertension (PH) is a hemodynamic and pathophysiological state that is classified according to the hemodynamic profile of the pulmonary circulation — pre-capillary, post-capillary, or both (Fig. 6.1). Common causes of pre-capillary PH are related to chronic thromboembolic PH and pulmonary arterial hypertension that can be found in three main forms: idiopathic pulmonary arterial hypertension, familial form, and PH associated with other risk factors and medical conditions, such as collagen vascular diseases. Pre- and post-capillary PH is caused by heart disease and lung disease. All types of PH share common pathological changes in the form of proliferative vasculopathy, characterized by vasoconstriction and cell proliferation. Left heart disease (WHO Group 2) is the most common cause of PH in Western countries. The second most common cause of PH is WHO Group 3 that is comprised of lung disease associated with hypoxia and sleep-disordered breathing. Owing to their high prevalence, sleep-disordered breathing and chronic obstructive pulmonary disease (COPD) are by far the most common causes of PH in Group 3. Obstructive sleep apnea (OSA) is the most common form of sleep-disordered breathing, affecting up to 50% of men and 25% of women in the middle-aged population [1, 2]. In general, 27–30% of patients with OSA without left ventricular dysfunction or hypoxemic lung disease have PH, which tends to be mild to moderate in severity. However, severe PH can occur in the setting of OSA [3–5]. Nocturnal hypoxemia can be an important indicator of the presence of PH in this population. Patients with OSA and PH have a worse prognosis with a lower quality of life and higher mortality than those without PH. Treatment of OSA is associated with decreased pulmonary artery pressure (Ppa).

V. Mohsenin (✉)
Section of Pulmonary, Critical Care and Sleep Medicine, Yale University, New Haven, CT, USA
e-mail: Vahid.mohsenin@yale.edu

C. Won (ed.), *Complex Sleep Breathing Disorders*,
https://doi.org/10.1007/978-3-030-57942-5_6

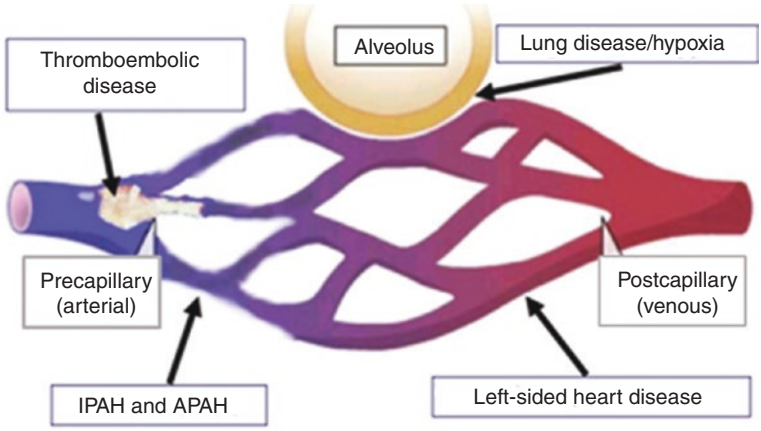


Fig. 6.1 Major causes of pre-capillary PH are related to pulmonary arterial hypertension and chronic thromboembolic PH. Common causes of post-capillary pulmonary hypertension are left-sided heart disease, lung disease, and hypoxia

Case Report

A 40-year-old man was seen in the pulmonary clinic because of increasing dyspnea and excessive daytime sleepiness. The patient gave a history of habitual snoring and unrefreshing sleep with daytime fatigue for approximately 3 years before the clinic visit. Shortness of breath on exertion developed about a year ago. The patient reported gasping awake occasionally, heartburn, and one- to two-time nocturia.

On examination, the patient appeared comfortable. The blood pressure was 158/92 mm Hg, the pulse 88 beats per minute, and the oxygen saturation 96% while he was breathing ambient air. The height was 171.5 cm, the weight was 91.6 kg, and the body mass index was 31 kg/m^2. The upper airway examination showed narrowed oropharyngeal inlet due to increased soft tissue mass. Neck circumference was 40 cm. The jugular veins were not visible due to a short neck. Heart sounds were distant, without a murmur, rub, or gallop, and lungs were clear. There was leg edema to the knees; the remainder of the examination was normal. The complete blood count and serologic testing for collagen vascular disease were essentially normal. An electrocardiogram (ECG) showed sinus rhythm at a rate of 92 beats per minute and right axis deviation. Echocardiogram showed normal left ventricular cavity size, hyperdynamic left ventricular systolic function, and moderate concentric left ventricular hypertrophy. Left ventricular ejection fraction was >70%. Left ventricular ejection fraction was >70% with mildly decreased right ventricular systolic function; the right ventricular systolic pressure (RVSP) was estimated to be 65 mm Hg. Right and left atria were mildly dilated. The chest radiograph showed enlargement of the right, left, and main pulmonary arteries. The lungs were clear, with no evidence of interstitial lung disease or emphysema. A CT scan of the chest and a subsequent pulmonary CT angiogram confirmed the enlargement of the main

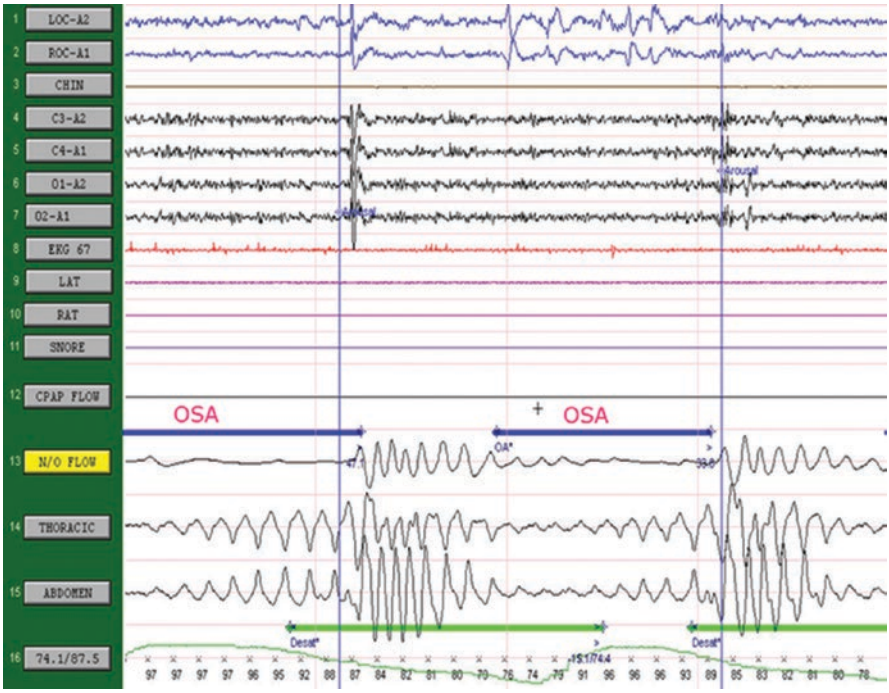


Fig. 6.2 A polysomnograph of 60 s in duration shows two obstructive apneas during REM sleep with oxygen desaturations to a nadir of 74%

pulmonary artery and no evidence of pulmonary emboli. The right ventricle was enlarged; the wall of the right ventricle was thick (5 mm), with flattening of the inter-ventricular septum. Polysomnography was performed. A 60-s epoch of the polysomnography shows two obstructive apneas during REM sleep with oxygen desaturations to a nadir of 74% (Fig. 6.2). Apnea-hypopnea index (AHI) was 29 events per hour with mean asleep arterial oxygen saturation of 94%, and time with oxygen saturation below 90% was 36 min.

Discussion

Mechanism of PH in OSA

Many patients with OSA experience cyclical oxygen desaturations during sleep. The cumulative effect of intermittent hypoxia can lead to PH [6, 7]. Most patients with OSA have normal oxygen saturation while awake, apart from those patients who also have an obesity-hypoventilation syndrome or underlying lung disease.

Left ventricular dysfunction accounts for a large proportion of PH in patients with OSA [8–12]. However, PH and right heart failure can develop in patients with OSA with preserved left ventricular ejection fraction [13]. The prevalence of PH in heart failure with preserved left ventricular ejection fraction (HFpEF) was reported in the range of 52% (defined as mean Ppa >25 mmHg by right heart catheterization) [14]. This prevalence was comparable to 62% in a cohort of 379 patients with heart failure with reduced ejection fraction (HFrEF), who had a mean Ppa >20 mmHg by right heart catheterization [15]. Mathematical models demonstrate that there is an initial passive increase in pulmonary blood volume secondary to the hydrostatic forces resulting from heart failure with either reduced or preserved systolic function [13]. The result of this initial insult is a passive post-capillary PH with a normal transpulmonary pressure gradient and, consequently, relatively normal pulmonary vascular resistance. Over time, long-standing venous PH results in pulmonary arterial endothelial dysfunction, leading to elevated levels of endothelin-1, decreased nitric oxide levels, and a decrease in brain natriuretic peptide-mediated vasodilatation [16]. These biochemical changes result in active pulmonary arterial vasospasm, leading to a further increase in pulmonary arterial pressures. In addition to this pressure-dependent mechanism, hypoxia-sensitive inflammatory and proliferative pathways may be involved in the development of PH in OSA [17]. Animal models have demonstrated that brief, repetitive exposure to hypoxemia over just a few weeks, a situation akin to intermittent hypoxia in OSA, is sufficient to cause pulmonary arteriolar remodeling and right ventricular hypertrophy [18, 19]. A meta-analysis of 16 studies demonstrated right ventricular hypertrophy and enlargement and decreased right ventricular ejection fraction in patients with OSA [20]. Continuous monitoring of Ppa in OSA patients showed a gradual rise in mean Ppa throughout nighttime sleep compared with snorers-only subjects [21].

Diagnostic Considerations

The evaluation process for a patient with suspected PH requires a series of investigations intended to confirm the diagnosis, which is best done in a multidisciplinary pulmonary vascular center. Patients with PH may be asymptomatic or present with symptoms of dyspnea, lightheadedness on exertion, fatigue, chest pain, syncope, palpitations, and/or lower extremity edema. However, patients with suspected OSA and PH may not have these symptoms. Transthoracic echocardiography provides several variables that correlate with right heart hemodynamics, including estimated systolic Ppa, and should always be performed in the case of suspected PH as a screening modality. A systematic review and meta-analysis of 29 studies with a total patient population of 1998 demonstrated an overall correlation coefficient of 0.70 (95% confidence interval [CI], 0.67–0.73) for estimated systolic Ppa between color Doppler echocardiography (tricuspid regurgitant jet method) and right heart catheterization, with a sensitivity and specificity of 83% (95% CI, 73–90%) and 72% (95% CI, 53–85%), respectively [22]. Of note, the agreement between Doppler

echocardiography and right heart catheterization data was similar at both mild and moderately elevated systolic Ppa values. Right heart catheterization is confirmatory, yields more precise pressure measurements, and allows assessment of the vasodilatory capacity of pulmonary vasculature that can help guide therapy (Fig. 6.3). PH is defined hemodynamically by right heart catheterization by a mean Ppa greater than or equal to 25 mm Hg at rest [23]. However, in the recent World Symposium on Pulmonary Hypertension 2018 in Nice, the definition of PH was revised: "Based on data from normal subjects, the normal mean pulmonary arterial pressure (mPAP) at rest is approximately 14.0 ± 3.3 mm Hg [24]. Two standard deviations above this mean value would indicate that an mPAP >20 mmHg is the threshold for abnormal pulmonary arterial pressure (above the 97.5th percentile). However, this level of mPAP is not sufficient to define pulmonary vascular disease since it could be due to increases in cardiac output or pulmonary artery wedge pressure (PAWP). The task force has, therefore, proposed including a pulmonary vascular resistance (PVR) ≥3 WU into the definition of pre-capillary PH associated with mPAP >20 mmHg, irrespective of etiology" [25]. Pulmonary artery occlusion pressure (PAOP or PAWP) of greater than 15 mm Hg denotes elevated left ventricular pressure, in either HFrEF or HFpEF. Pulmonary artery diastolic pressure gradient (DPG = diastolic Ppa – PAOP) distinguishes pre-capillary (≥7 mm Hg) and post-capillary (<7 mm Hg) PH in setting of normal or reduced left ventricular ejection fraction. The combination of Ppa ≥ 25 mm Hg, PAOP > 15 mm Hg, and DPG ≥ 7 mm Hg indicates combined pre- and post-capillary (pulmonary venous) PH (Fig. 6.3) [26].

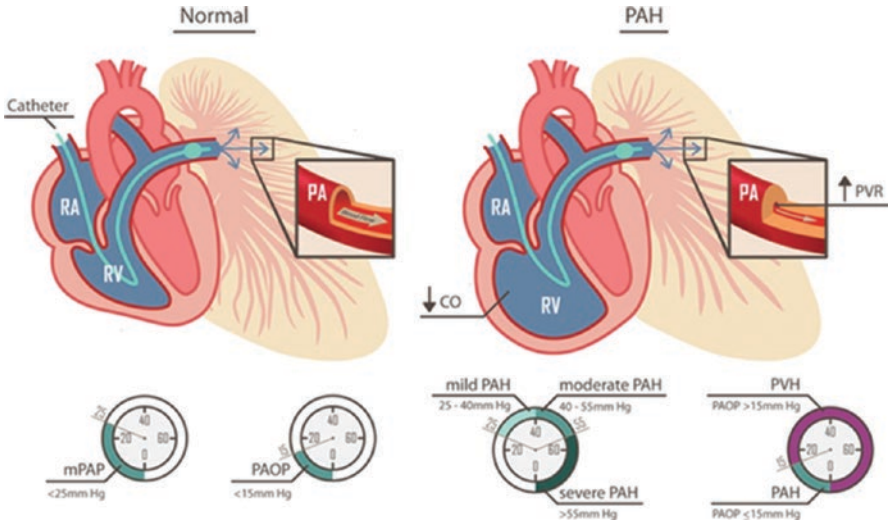


Fig. 6.3 Right heart catheterization hemodynamics in normal and in pulmonary arterial hypertension (PAH). PVH, pulmonary venous hypertension; CO, cardiac output; mPAP, mean pulmonary artery pressure; PAOP, pulmonary artery occlusion pressure; PVR, pulmonary vascular resistance. The 2018 proposed definition of PH is mPAP >20 mm Hg and PVR ≥3.0 WU [25]

There are no formal guidelines for routine sleep study in patients with PH; however, given the high prevalence of nocturnal hypoxemia and OSA in patients with PH [27], patients with PH should be screened for sleep-disordered breathing by a sleep study. Other diagnostic tests may include serologic testing for collagen vascular diseases, pulmonary function tests, chest imaging, ventilation-perfusion scanning, and arterial blood gases for underlying pulmonary diseases.

Effect of Treatment of OSA on PH

The studies on the effect of treatment of OSA on pulmonary hemodynamics and PH are limited. Treatment with continuous positive airway pressure (CPAP) for 6 months in six patients with OSA and PH diagnosed on echocardiography and confirmed by right heart catheterization with normal PAOP values reduced mean Ppa values from 25.6 ± 4.0 mm Hg to 19.5 ± 1.6 mm Hg ($P < 0.001$) [3]. In a prospective study involving 22 patients with OSA (mean AHI, 48.6 ± 5.2 events/h), five of whom had mean Ppa 20 mm Hg, 4 months of CPAP treatment decreased mean Ppa from 17.0 ± 1.2 mm Hg to 14.5 ± 0.8 mm Hg in the entire group ($P < 0.05$). The most significant treatment effects occurred in the five patients who had PH at baseline. The reduction in mean Ppa was attributed to decreased pulmonary vascular resistance and decreased vasoconstrictive response to a hypoxic stimulus [28]. In a randomized, sham-controlled cross-over study involving ten patients with OSA and PH (RVSP > 30 mm Hg estimated by Doppler echocardiography) and no known cardiac or lung diseases, 12 weeks of CPAP therapy decreased RVSP from 28.8 ± 7.9 mm Hg to 24.0 ± 5.8 mm Hg ($P < 0.0001$) [29]. Higher reduction in RVSP after effective CPAP therapy was observed in patients with OSA with either left ventricular diastolic dysfunction (change, 7.3 ± 3.3 mm Hg vs. 1.6 ± 1.8 mm Hg in those without left ventricular diastolic dysfunction; $P < 0.001$) or presence of PH at baseline (change, 8.5 ± 2.8 mm Hg vs. 2.6 ± 2.8 mm Hg in those without PH at baseline; $P < 0.001$) [29]. In a meta-analysis of 7 studies with 222 patients (mean age of 52.5 years) with OSA and AHI of greater than 10 events/h (mean AHI of 58 events/h) and PH, defined as Ppa >25 mm Hg (mean Ppa of 39.3 ± 6.3 mm Hg), CPAP treatment for 3 to 70 months was associated with a decrease in Ppa of 13.3 mm Hg (95% CI 12.7–14.0) [30]. CPAP therapy for 6–24 months improved right ventricular ejection fraction estimated by nuclear ventriculography, which increased from 30% ± 3% to 39% ± 3% ($P < 0.01$) [31]. Based on currently available data, we recommend the treatment of mild-to-moderate PH with OSA-specific therapy for 6 months with follow-up echocardiography and consideration for the addition of pharmacotherapy in those with severe PH.

The index patient was treated with CPAP, and follow-up echocardiography after 6 months showed RVSP had decreased from 65 mm Hg to 50 mm Hg with the patient reporting some improvement in shortness of breath during exertion. Because of evidence for the persistence of PH and residual symptoms, right heart catheterization was performed for consideration of PH-specific treatment.

Clinical Pearls and Pitfalls

- OSA is a highly prevalent sleep-disordered breathing that is associated with an increased risk of cardio-cerebrovascular complications and increased mortality.
- PH is a common comorbid disorder in a patient with OSA and, in large part, related to nocturnal hypoxemia and left ventricular dysfunction.
- Patients with OSA, especially those with daytime hypoxemia and hypercapnia or significant nocturnal oxygen desaturations, should be screened for PH by echocardiography.
- Treatment of OSA with CPAP therapy improves PH.

References

1. Franklin KA, Lindberg E. Obstructive sleep apnea is a common disorder in the population-a review on the epidemiology of sleep apnea. J Thorac Dis. 2015;7(8):1311–22.
2. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med. 2015;3(4):310–8.
3. Alchanatis M, Tourkohoriti G, Kakouros S, Kosmas E, Podaras S, Jordanoglou JB. Daytime pulmonary hypertension in patients with obstructive sleep apnea: the effect of continuous positive airway pressure on pulmonary hemodynamics. Respiration. 2001;68(6):566–72.
4. Bady E, Achkar A, Pascal S, Orvoen-Frija E, Laaban JP. Pulmonary arterial hypertension in patients with sleep apnoea syndrome. Thorax. 2000;55(11):934–9.
5. Sajkov D, McEvoy RD. Obstructive sleep apnea and pulmonary hypertension. Prog Cardiovasc Dis. 2009;51(5):363–70.
6. Kholdani C, Fares WH, Mohsenin V. Pulmonary hypertension in obstructive sleep apnea: is it clinically significant? A critical analysis of the association and pathophysiology. Pulm Circ. 2015;5(2):220–7.
7. Mohsenin V. The emerging role of microRNAs in hypoxia-induced pulmonary hypertension. Sleep Breath. 2016;20(3):1059–67.
8. Hetzel M, Kochs M, Marx N, Woehrle H, Mobarak I, Hombach V, et al. Pulmonary hemodynamics in obstructive sleep apnea: frequency and causes of pulmonary hypertension. Lung. 2003;181(3):157–66.
9. Oudiz RJ. Pulmonary hypertension associated with left-sided heart disease. Clin Chest Med. 2007;28(1):233–41, x.
10. Minai OA, Ricaurte B, Kaw R, Hammel J, Mansour M, McCarthy K, et al. Frequency and impact of pulmonary hypertension in patients with obstructive sleep apnea syndrome. Am J Cardiol. 2009;104(9):1300–6.
11. Strange G, Playford D, Stewart S, Deague JA, Nelson H, Kent A, et al. Pulmonary hypertension: prevalence and mortality in the Armadale echocardiography cohort. Heart. 2012;98(24):1805–11.
12. Hansdottir S, Groskreutz DJ, Gehlbach BK. WHO's in second?: a practical review of World Health Organization group 2 pulmonary hypertension. Chest. 2013;144(2):638–50.
13. Segers VF, Brutsaert DL, De Keulenaer GW. Pulmonary hypertension and right heart failure in heart failure with preserved left ventricular ejection fraction: pathophysiology and natural history. Curr Opin Cardiol. 2012;27(3):273–80.

14. Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. J Am Coll Cardiol. 2009;53(13):1119–26.
15. Ghio S, Gavazzi A, Campana C, Inserra C, Klersy C, Sebastiani R, et al. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. J Am Coll Cardiol. 2001;37(1):183–8.
16. Moraes DL, Colucci WS, Givertz MM. Secondary pulmonary hypertension in chronic heart failure: the role of the endothelium in pathophysiology and management. Circulation. 2000;102(14):1718–23.
17. Voelkel NF, Mizuno S, Bogaard HJ. The role of hypoxia in pulmonary vascular diseases: a perspective. Am J Physiol Lung Cell Mol Physiol. 2013;304(7):L457–65.
18. McGuire M, Bradford A. Chronic intermittent hypercapnic hypoxia increases pulmonary arterial pressure and haematocrit in rats. Eur Respir J. 2001;18(2):279–85.
19. Campen MJ, Shimoda LA, O'Donnell CP. Acute and chronic cardiovascular effects of intermittent hypoxia in C57BL/6J mice. J Appl Physiol (1985). 2005;99(5):2028–35.
20. Maripov A, Mamazhakypov A, Sartmyrzaeva M, Akunov A, Muratali Uulu K, Duishobaev M, et al. Right ventricular remodeling and dysfunction in obstructive sleep apnea: a systematic review of the literature and meta-analysis. Can Respir J. 2017;2017:1587865.
21. Sforza E, Laks L, Grunstein RR, Krieger J, Sullivan CE. Time course of pulmonary artery pressure during sleep in sleep apnoea syndrome: role of recurrent apnoeas. Eur Respir J. 1998;11(2):440–6.
22. Janda S, Shahidi N, Gin K, Swiston J. Diagnostic accuracy of echocardiography for pulmonary hypertension: a systematic review and meta-analysis. Heart. 2011;97(8):612–22.
23. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Rev Esp Cardiol (Engl Ed). 2016;69(2):177.
24. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. Eur Respir J. 2009;34(4):888–94.
25. Galie N, McLaughlin VV, Rubin LJ, Simonneau G. An overview of the 6th world symposium on pulmonary hypertension. Eur Respir J. 2019;53(1):1802148. https://doi.org/10.1183/13993003.02148-2018.
26. Gerges C, Gerges M, Lang MB, Zhang Y, Jakowitsch J, Probst P, et al. Diastolic pulmonary vascular pressure gradient: a predictor of prognosis in "out-of-proportion" pulmonary hypertension. Chest. 2013;143(3):758–66.
27. Jilwan FN, Escourrou P, Garcia G, Jais X, Humbert M, Roisman G. High occurrence of hypoxemic sleep respiratory disorders in precapillary pulmonary hypertension and mechanisms. Chest. 2013;143(1):47–55.
28. Sajkov D, Wang T, Saunders NA, Bune AJ, McEvoy RD. Continuous positive airway pressure treatment improves pulmonary hemodynamics in patients with obstructive sleep apnea. Am J Respir Crit Care Med. 2002;165(2):152–8.
29. Arias MA, Garcia-Rio F, Alonso-Fernandez A, Martinez I, Villamor J. Pulmonary hypertension in obstructive sleep apnoea: effects of continuous positive airway pressure: a randomized, controlled cross-over study. Eur Heart J. 2006;27(9):1106–13.
30. Imran TF, Ghazipura M, Liu S, Hossain T, Ashtyani H, Kim B, et al. Effect of continuous positive airway pressure treatment on pulmonary artery pressure in patients with isolated obstructive sleep apnea: a meta-analysis. Heart Fail Rev. 2016;21(5):591–8.
31. Nahmias J, Lao R, Karetzky M. Right ventricular dysfunction in obstructive sleep apnoea: reversal with nasal continuous positive airway pressure. Eur Respir J. 1996;9(5):945–51.

Chapter 7
Primary Central Sleep Apnea

Anan Salloum and M. Safwan Badr

Case

A 50-year-old man presented to the sleep clinic complaining of frequent awakenings and insomnia for 1 year. The patient's bed partner reported mild snoring and witnessed apneic episodes. The patient denied difficulty falling asleep, dyspnea, orthopnea, or leg swelling. The patient had no neurological symptoms or muscular weaknesses. The patient had no significant medical history and reported no medication use. He denied using narcotics or illicit drugs.

On physical examination, the patient was non-obese with a body mass index of 26 kg/m^2. The patient's heart rate was 70 beats/min, blood pressure 130/70 mmHg, and O_2 saturation 97% or room air. Lungs were clear to auscultation, and cardiac exam showed regular rate and rhythm with normal heart sounds without murmurs or gallops. No lower extremity edema was noted. Neurological exam showed no neurological deficit or muscle weakness.

Polysomnography showed an apnea-hypopnea index (AHI) of 32 events/h with a central apnea index (CAI) of 20 events/h (78% of AHI events were central in nature). Most events were seen in sleep stages N1 and N2. No events were seen in rapid eye movement (REM) sleep. Example of central apneas seen is in Fig. 7.1. The remainder of the events consisted of obstructive hypopneas. No Cheyne-Stokes breathing pattern was observed. Central apneas were short in duration, lasting approximately 15 s and terminating with an arousal and an abrupt respiratory effort. Central and

A. Salloum
Wayne State University, John D. Dingell VA Medical Center, Detroit, MI, USA

M. S. Badr (✉)
Department of Internal Medicine, Wayne State University School of Medicine, University Health Center, Detroit, MI, USA
e-mail: sbar@med.wayne.edu

C. Won (ed.), *Complex Sleep Breathing Disorders*,
https://doi.org/10.1007/978-3-030-57942-5_7

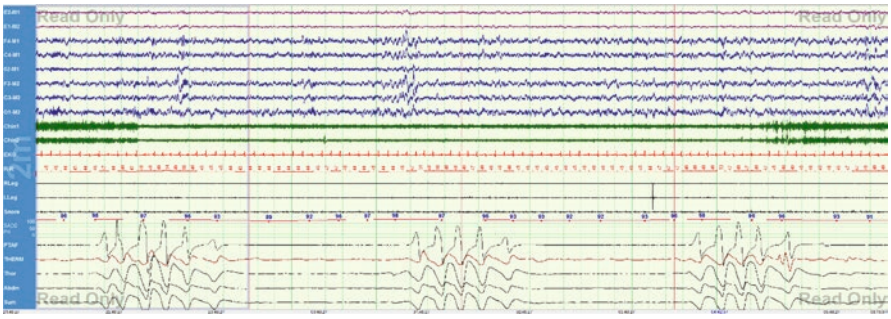


Fig. 7.1 A representative polysomnography segment showing central apneas (without Cheyne-Stokes respiration). Note the absence of flow and effort as evidenced by the absence of thoracic and abdominal signal on respiratory inductance plethysmography (RIP). In primary central sleep apnea, the inter-apnea or ventilatory phase is typically short lasting 2–5 breaths, and do not have the crescendo-decrescendo pattern seen with Cheyne-Stokes breathing. These central apneas may lead to arousals, and commonly lead to mild arterial oxygen desaturations, although severede-saturations may also be seen. Central apneas are less common during REM sleep

obstructive events were associated with sleep fragmentation, and many post-arousal central apneas were also observed. Because the patient was symptomatic, it was decided to proceed with a trial of therapy. During a titration study, continuous positive airway pressure therapy (CPAP) of 10 cmH_2O eliminated most obstructive and central respiratory events.

Given the severity of central apnea, the patient had brain magnetic resonance imaging (MRI) which did not reveal any neurological pathology such as Chiari malformation. It was noted that the patient's serum bicarbonate level was low-normal at 23 mEq/L. The patient was diagnosed with primary (idiopathic) central sleep apnea and obstructive sleep apnea. He was treated with CPAP of 10 cmH_2O and reported significant improvement in daytime sleepiness.

Discussion

Definition

Central sleep apnea (CSA) is characterized by the repetitive cessation of breathing due to loss of ventilatory motor output. Central events are defined by cessation or reduction of airflow during sleep lasting >10 s, matched with an absence or reduction of inspiratory effort [1]. While central apneas are readily distinguishable from obstructive events, central hypopneas are difficult to identify on standard polysomnography. The American Academy of Sleep Medicine (AASM) scoring guidelines suggest central hypopneas may be scored if there is an absence of obstructive

features such as snoring, flow limitation, or paradoxical thoraco-abdominal movements. However, even with these guidelines, obstructive and central hypopneic events are difficult to distinguish, and many sleep centers choose not to score central hypopneas. Furthermore, in many instances, obstructive and central apneas/hypopneas co-occur. In other words, the upper airway may collapse during a central event, or there may be reduced ventilatory effort during an obstructive event. The International Classification of Sleep Disorders – Third Edition (ICSD-3) defines central sleep apnea arbitrarily as having >5 events/h, with the central component comprising more than 50% of the total AHI. Importantly, in order to be considered a syndrome, there need to be associated clinical manifestations. It is unclear whether our current definition of disease best captures clinical outcomes and best dictates treatment.

Central apneas occur under several conditions, and in order to deem them idiopathic or primary, a concomitant disorder needs to be ruled out. Pathophysiologically, CSA may be considered as hypercapnic vs normo-/hypocapnic. The normo- or hypocapnic CSA phenotype is associated with Cheyne-Stokes breathing, high-altitude periodic breathing, treatment-emergent central sleep apnea, and primary CSA. The hypercapnic CSA phenotype is associated with hypoventilatory conditions such as that associated with neuromuscular disease or medications or opioid use.

Epidemiology and Demographics

Central sleep apnea overall is less prevalent than obstructive apnea. A cross-sectional analysis of baseline data from 5804 participants of the Sleep Heart Health Study showed the prevalence of CSA (undifferentiated) in this general population sample was 0.9% (95% confidence intervals [CI]: 0.7–1.2). Individuals with CSA were older, had lower BMI, had lower Epworth Sleepiness Scale score, and were more likely to be male than individuals with obstructive sleep apnea [2]. Primary central sleep apnea is even less common. Because of the rarity of the disease, demographic data is lacking, though it is believed it tends to be more common in middle-aged and elderly men.

Pathophysiology of Primary Central Sleep Apnea

The removal of the wakefulness drive to breathe renders respiration during sleep critically dependent on arterial PCO_2, particularly during NREM sleep. Consequently, normo- or hypocapnic central apnea occurs if arterial PCO_2 is lowered below a highly sensitive “apneic threshold” [3, 4]. A central apnea is often followed by hypoxemia and a transient arousal [5, 6]. There is sympathetic stimulation, and

often an exaggerated ventilatory response ensues. Hyperventilation overshoots the arterial PCO_2 below the apneic threshold leading to cycling of more central events. In fact, patients with primary (idiopathic) central apnea have demonstrated increased ventilatory responsiveness to changes in arterial PCO_2 (i.e., high loop gain) [7].

Ventilation during NREM sleep, particularly N1 and N2 sleep, is sensitive to arterial PCO_2 changes. As a result, normo- and hypocapnic central apneas (i.e., those due to high loop gain) are most frequent during these stages of sleep. Meanwhile, the control of respiration during N3 and REM sleep is less dependent on arterial PCO_2 and PO_2, and therefore, central apneas are rarely seen during these sleep stages. Central apneas related to hypoventilation or hypercapnia, on the other hand, may be observed during REM sleep and particularly during phasic REM sleep.

Clinical Signs and Symptoms

The presenting symptoms in patients with primary central apnea are variable. Presenting symptoms may be similar to obstructive sleep apnea including snoring and excessive daytime sleepiness. Alternatively, some patients with central sleep apnea may present with insomnia and poor nocturnal sleep. This may be due to frequent oscillation between wakefulness and stage 1 NREM sleep. It is important to note, however, that most of the data on the presentation of central sleep apnea are based on reports of small numbers of patients.

Patients with primary central sleep apnea are usually not obese. Their symptoms include insomnia, disturbed sleep, witnessed apneas, and daytime sleepiness. Snoring is usually milder than snoring associated with obstructive sleep apnea. Physical exam usually lacks signs suggestive of pulmonary, cardiac, or neuromuscular disease. If arterial blood gas is drawn, a low-normal PCO_2 is observed [7]. The correlate would be low-normal serum bicarbonate levels, which results from chronic mild respiratory alkalemia.

Treatment

There are no treatment guidelines specific to primary central sleep apnea. The decision to treat a patient with CSA is made on the combination of clinical symptoms, polysomnographic findings, and clinical experience and judgment. The lack of prospective outcome data or accepted metrics of severity renders simple algorithms difficult to implement. Furthermore, comorbid conditions, such as obstructive sleep apnea, influence the therapeutic approach. Most of the recommendations for primary CSA are extrapolated from studies on patients with CSA and heart failure.

The AASM Practice Parameters for treatment of primary central sleep apnea include positive airway pressure (PAP) and medications such as acetazolamide,

zolpidem, and triazolam [8]. Although no randomized control trials have tested the effectiveness of PAP in the treatment of primary central sleep apnea, PAP in the form of CPAP, bilevel PAP with a backup rate (e.g., BPAP-ST), and adaptive servo-ventilation (ASV) are commonly used to treat this condition. CPAP is likely to work by increasing lung volume, dampening ventilator overshoot, and preventing concomitant upper airway narrowing [5, 9]. A trial of CPAP is generally recommended as a first-line therapy as it is effective in about 50% of patients. Conversely, bilevel PAP may worsen central apnea unless used with a backup rate, since bilevel PAP may augment ventilation excessively during spontaneous breathing and cause ventilatory overshoot below the apneic threshold. Finally, ASV, a form of closed-loop mechanical ventilation, that differs from CPAP or bilevel PAP by providing dynamic adjustment of inspiratory pressure support with an automated backup rate may be highly effective in treating normo- or hypocapnic CSA. By delivering a preset minute ventilation, ASV mitigates post-apneic hyperventilation and decreases the frequency of central apnea. ASV may be considered in those who fail or are intolerant of CPAP. However, it is contraindicated in those with heart failure and reduced ejection fraction [10].

Pharmacologic therapy for central apnea is intuitively appealing but lacks long-term clinical trials. Available studies have investigated acetazolamide and hypnotics, mostly as short-term trials focusing on reduced frequency of respiratory events. Acetazolamide, a carbonic anhydrase inhibitor diuretic, induces metabolic acidosis and stimulates respiration by widening the apneic threshold. Its efficacy in primary CSA has been demonstrated in a small number of clinical trials. White et al. [11] administered acetazolamide to six patients with symptomatic central sleep apnea. All six patients had significant improvement, demonstrating a 69% reduction in total apneas. Five of the six patients reported better-quality sleep and decreased daytime hypersomnolence. Similarly, DeBacker et al. [12] used low-dose acetazolamide (250 mg/day, 1 h before sleep) and found CAI decreased during the first night of acetazolamide use and further reduced after 1 month of therapy. The number of arousals also decreased after 1 month of medication use. Overall, acetazolamide is considered an option but requires close clinical follow-up and knowledge about potential side effects including dizziness and increased urination.

The effectiveness of hypnotics on the treatment of central apnea was also investigated based on the premise that suppressing arousals may stabilize breathing. Quadri et al. [13] studied the effect of zolpidem on primary CSA in an open-label trial of 20 patients. Zolpidem use for 9 weeks was associated with decreased central apnea-hypopnea index, improved sleep continuity, and decreased subjective daytime sleepiness but worsening of obstructive apnea in three patients. While the aforementioned studies showed a salutary effect for both medications, the small number of participants, lack of long-term outcome data, and potential risk of side effects preclude recommendations regarding these agents as therapeutic intervention in primary CSA.

Supplemental oxygen has been used successfully in patients with CSA secondary to heart failure. The mechanisms underlying the effect of oxygen on ventilatory

control during sleep include reduction in controller gain, with improvement in overall loop gain or chemoresponsiveness. The role of supplemental oxygen in primary CSA however is unknown, and its use is often at the discretion of the clinician based on his or her experience.

Key Points

- Central sleep apnea is generally thought of in two categories: (1) normo- or hypocapnic and (2) hypercapnic CSA. In normo- or hypocapnic CSA, central apneas arise from high loop gain and unstable breathing. In the hypercapnic CSA phenotype, central apneas arise in the context of hypoventilation or ventilatory impairment, such as would be seen with neuromuscular disease or opioid use.
- CSA is associated with several conditions including heart failure, neuromuscular disease, opioid use, ascent to high altitude, and positive airway pressure use. CSA is considered idiopathic or primary when none of these associations are identified.
- Primary CSA is considered part of the normo- or hypocapnic phenotype. In primary CSA, apneas result from high loop gain, narrow apneic threshold window, increased arousal sensitivity, as well as increased ventilatory response to arousal.
- There are very little data about risk factors, or the clinical implications of primary CSA.
- Treatment decisions are generally driven by the patient's symptoms or by CSA severity.
- There are no good data regarding therapies for primary CSA. There is overlap in the pathophysiology and presentation of central and obstructive sleep apnea, making CPAP an appropriate initial therapy. Medications such as acetazolamide, theophylline, and triazolam have been studied and may have an effect of improving primary CSA. However, these medications come with many side effects, and close monitoring is often needed.
- There is no data about long-term clinical consequences of treated or untreated primary CSA, and treatment is often at the discretion of the clinician.
- Studies are needed to understand the pathophysiology and clinical implications of primary CSA and to determine the risks or benefits of therapy.

References

1. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. Deliberations of the sleep apnea definitions task Force of the American Academy of Sleep Medicine. J Clin Sleep Med. 2012;8(5):597–619.
2. Donovan LM, Kapur VK. Prevalence and characteristics of central compared to obstructive sleep apnea: analyses from the sleep heart health study cohort. Sleep. 2016;39(7):1353–9.
3. Chowdhuri S, Badr MS. Central sleep apnoea. Indian J Med Res. 2010;131:150–64.
4. Javaheri S, Dempsey JA. Central sleep apnea. Compr Physiol. 2013;3(1):141–63.
5. Badr MS, Toiber F, Skatrud JB, Dempsey J. Pharyngeal narrowing/occlusion during central sleep apnea. J Appl Physiol (1985). 1995;78(5):1806–15.
6. Xie A, Wong B, Phillipson EA, Slutsky AS, Bradley TD. Interaction of hyperventilation and arousal in the pathogenesis of idiopathic central sleep apnea. Am J Respir Crit Care Med. 1994;150(2):489–95.
7. Xie A, Rutherford R, Rankin F, Wong B, Bradley TD. Hypocapnia and increased ventilatory responsiveness in patients with idiopathic central sleep apnea. Am J Respir Crit Care Med. 1995;152(6 Pt 1):1950–5.
8. Aurora RN, Chowdhuri S, Ramar K, et al. The treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses. Sleep. 2012;35(1):17–40.
9. Issa FG, Sullivan CE. Reversal of central sleep apnea using nasal CPAP. Chest. 1986;90(2):165–71.
10. Aurora RN, Bista SR, Casey KR, et al. Updated adaptive servo-ventilation recommendations for the 2012 AASM guideline: “the treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses”. J Clin Sleep Med. 2016;12(5):757–61.
11. White DP, Zwillich CW, Pickett CK, Douglas NJ, Findley LJ, Weil JV. Central sleep apnea. Improvement with acetazolamide therapy. Arch Intern Med. 1982;142(10):1816–9.
12. DeBacker WA, Verbraecken J, Willemen M, Wittesaele W, DeCock W, Van deHeyning P. Central apnea index decreases after prolonged treatment with acetazolamide. Am J Respir Crit Care Med. 1995;151(1):87–91.
13. Quadri S, Drake C, Hudgel DW. Improvement of idiopathic central sleep apnea with zolpidem. J Clin Sleep Med. 2009;5(2):122–9.

Chapter 8
Treatment-Emergent Central Sleep Apnea

Andrey Zinchuk and Henry Klar Yaggi

Case

A 56-year-old man with a history of hypertension, paroxysmal atrial fibrillation, and well-controlled anxiety presents for evaluation of unrefreshing sleep. He reports 10 years of morning fatigue, waking up unrefreshed, and repeated middle of the night awakenings. This prevents him from carrying out his work responsibilities as an accountant efficiently, and he notes increasing irritability. He previously used zolpidem for 1 week, which improved his morning fatigue, but it caused headache and dizziness and was subsequently stopped. Intermittent snoring is noted by family. He denies symptoms of a hypersomnia or symptoms of restless legs syndrome. Review of systems is notable for a 10-pound weight gain. He has never smoked and reports consuming 0–1 alcoholic drinks per day. Family history is notable for coronary artery disease and stroke in his father. Medications include aspirin, metoprolol, and escitalopram.

On examination, body mass index is 29 kg/m^2, and neck circumference is 17 inches. He is normotensive with a heart rate of 88 beats/min with an irregularly irregular rhythm. He has normal dentition without overjet, enlarged (3+) tonsils, and a Mallampati classification of 3. The remainder of examination is normal. Laboratory studies are notable for hemoglobin of 14 mg/dL, bicarbonate of 24 mEq/L, and normal thyroid-stimulating hormone levels. Transthoracic echocardiogram reveals an enlarged left atrium, mild concentric left ventricular hypertrophy, an ejection fraction of 60%, and normal right heart size and function. Epworth sleepiness scale score is 9 of 24 and insomnia severity index is 22 of 28.

Given the high pretest probability of sleep apnea, a split-night polysomnography is performed (Fig. 8.1). The diagnostic portion of the study reveals an overall

A. Zinchuk (✉) · H. K. Yaggi
Pulmonary, Critical Care and Sleep Medicine, Yale University, New Haven, CT, USA
e-mail: andrey.zinchuk@yale.edu

C. Won (ed.), *Complex Sleep Breathing Disorders*,
https://doi.org/10.1007/978-3-030-57942-5_8

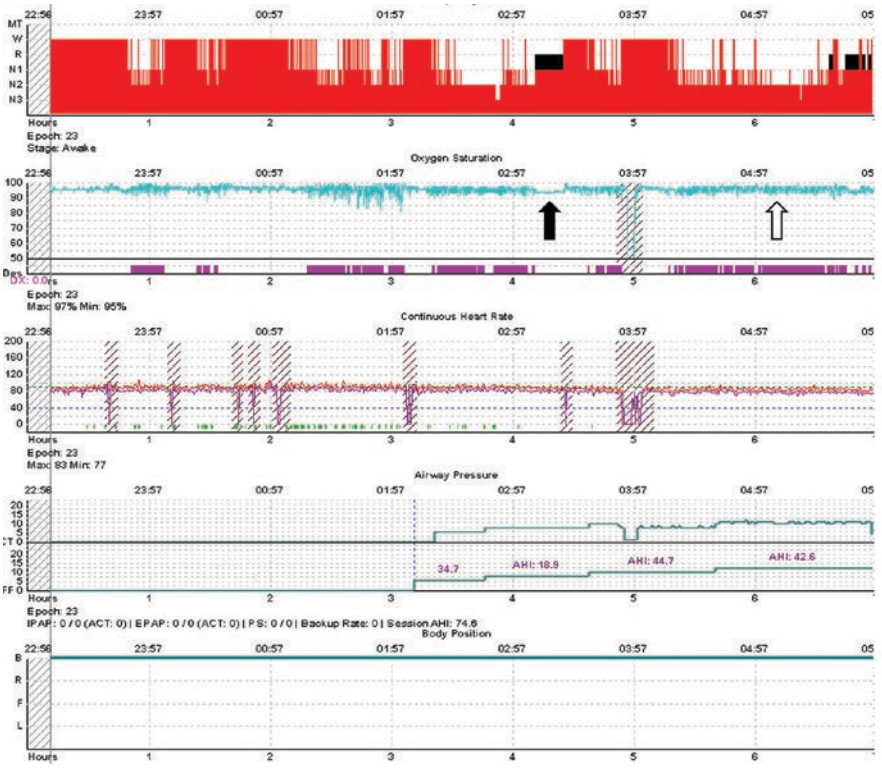


Fig. 8.1 Study hypnogram showing the patterns of treatment-emergent central sleep apnea on a split polysomnogram. Notice the non-rapid eye movement (NREM) predominance of events during application of continuous positive airway pressure and characteristic improvement in REM sleep (filled arrow). Deoxygenation tracing shows characteristic "zipper" pattern of periodic breathing and elevated loop gain sleep apnea (open arrow)

apnea-hypopnea index with 4% oxygen desaturations (AHI 4%) of 43 events/h and markedly fragmented sleep, with entire recording in supine position. Of note, >60% of events were hypopneas in non-rapid eye movement (NREM) sleep. These events show clear periodicity with associated obstruction. The nadir O_2 saturation is 83%. Upon initiation of continuous positive airway pressure (CPAP) via a nasal mask, the obstructive AHI 4% declined to 4/h at a pressure setting of 8 cmH_2O. There is minimal leak. However, significant central apneic events developed (central apnea index (CAI) of 36/h) with periodic breathing at an average cycle length of 30 s comprising >30% of recording time (Fig. 8.2). The duty ratio calculation (duration of ventilation divided by cycle duration [sum of ventilatory and apneic phases]) estimates loop gain at 2.1. Desaturations appear with a "zipper pattern" on the oximetry signal (Fig. 8.1). Respiratory events resolve during a 15-min period of REM sleep. Arousals tend to occur at the center of recovery breaths with an overall arousal index of 40/h, although sleep efficiency is improved. Post-study, the patient reports no marked change in sleepiness or energy level. Treatment-emergent central sleep

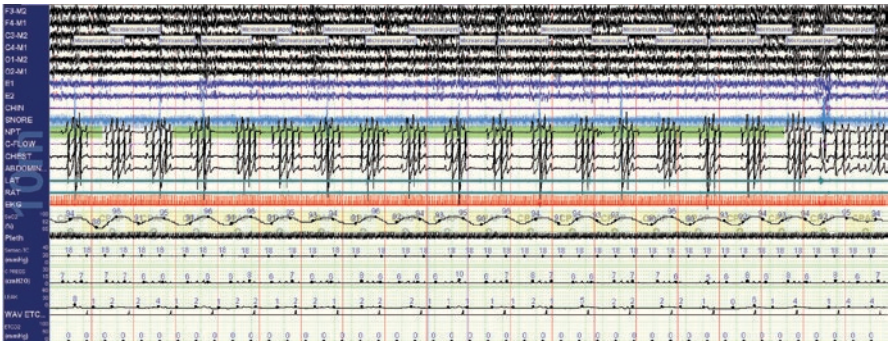


Fig. 8.2 Treatment-emergent central apneas (TE-CSA) while on continuous positive airway pressure (CPAP). Ten-minute screen compression; each vertical line is 30 s. Note the recurrent central apneas and periodic breathing with a cycle length of approximately 30 s, shorter than in those with heart failure central apneas with Cheyne-Stokes breathing (cycle length 60–90 s). Note characteristic arousals at the termination of central apneas, and marked sleep fragmentation

apnea (TE-CSA) with associated atrial fibrillation is diagnosed. He also has evidence of easy arousability estimated by a low arousal threshold (predicted by O_2 nadir of >83% and fraction of hypopneas >56%) and elevated loop gain (>1, based on duty ratio measurements).

The patient's goal is to improve his symptoms of sleep maintenance insomnia and fatigue. Auto-positive airway pressure (PAP) at a pressure setting of 8–12 cmH_2O with a nasal mask and lateral sleep are prescribed. CPAP acclimation therapy with respiratory therapist is completed over the ensuing 2 weeks. After 4 weeks, a minimal improvement in symptoms of insomnia and fatigue is noted, and the patient reports difficulty tolerating auto-PAP: "It just wakes me up at night and I don't feel like I get enough air." Review of the PAP download data shows minimal leak, average use of 4.2 h per night, 90th percentile pressure of 9 cmH_2O with a total residual machine AHI of 23/h, a clear airway index of 20/h, and 35% of total monitoring time spent in periodic breathing.

A discussion ensues with the patient regarding the risks and benefits of targeted treatment including adaptive servo-ventilation (ASV) and adjunctive therapies such as carbon dioxide (CO_2) rebreathing, acetazolamide, and hypnotics. A decision is made to pursue ASV supplemented by a trial of CO_2 rebreathing or acetazolamide as needed. Given his prior adverse experience with sedative hypnotics, benzodiazepine use is avoided. Based on a laboratory-based therapeutic study, ASV is titrated to the following settings: expiratory pressure of 6–10 cmH_2O, pressure support of 0–10 cmH_2O, and automatic respiratory rate. This results in marked improvement in measures of sleep-disordered breathing. The nadir O_2 saturation is 87%, the end-tidal CO_2 (ET_{CO2}) is 37 mmHg (36 mmHg at study start, off PAP), and the AHI and CAI decreased to 7 and 5 events/h, respectively, as measured by total flow in the system (C-flow, Fig. 8.3). However, there is ongoing respiratory instability manifested as pressure cycling (fluctuation of pressure support) and associated arousals (Fig. 8.3). These findings do not improve through the 3 h of ASV titration. A

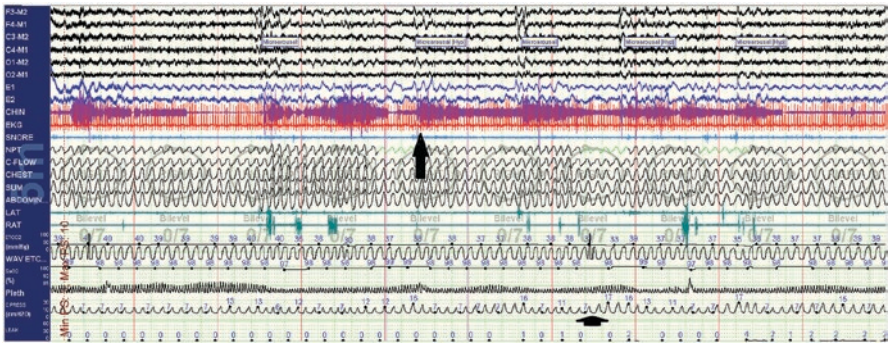


Fig. 8.3 Pressure cycling during adaptive ventilation treatment with nearly normal flow. Five-minute compression snapshot showing pressure cycling (arrow head). The C-PRESS channel is the pressure output from the adaptive ventilator. This 56-year-old man had predominantly central apneas, which were eliminated. However, repetitive arousals (arrow) and pressure cycling continued without resolution, despite adjustments of pressure support. There are few scorable respiratory events using C-flow signal (total flow in the system), and device may not automatically detect respiratory events during such periods (Adapted from Gunn et al., Sleep, 2008, 1–12, with permission)

non-ventilated mask is added, with increase in ET_{CO2} to 40 mmHg on the same ASV settings. The pressure cycling resolves with the residual AHI and CAI (measured using pressure signal of the ventilator) now equal to 3/h and 1/h. This includes supine sleep. Arousal index is 11/h. Thirty minutes of REM sleep is achieved with a residual obstructive AHI of 2/h. Some improvement of fatigue is noted the morning after titration study, and the patient reports his tolerance of ASV treatment is much improved compared to CPAP.

The patient is prescribed ASV at above settings using a non-vented mask. Two weeks later, a review of ASV download data showed a residual AHI and CAI of 3/h and <1/h, respectively, with just 5–10% of the night spent in periodic breathing. He uses PAP on average of 6.2 h/night for the last 7 consecutive days. The patient relates improvement in fatigue, decreased irritability, and uninterrupted sleep. ESS score is decreased to 7 and ISI score is now 11. His efficiency at work is improved. Repeat basic metabolic panel after 4 weeks of therapy shows a bicarbonate of 25 mEq/L.

Discussion Section

Introduction

As evident in this patient's case, in some with obstructive sleep apnea (OSA), central apneas and periodic breathing "emerge" with restoration of upper airway patency (Fig. 8.2). This phenomenon is termed treatment-emergent central sleep

apnea (TE-CSA). Initially described as "complex sleep apnea," the existence of TE-CSA as a unique clinical syndrome has been debated because of the varied natural history and clinical heterogeneity of the patients, reflective of the many causes of central sleep apnea (CSA) [1, 2]. This debate notwithstanding, it is becoming clear that in patients who exhibit TE-CSA, PAP uptake and adherence is poor in comparison to those with classic OSA, if the appropriate treatment is not selected [3, 4]. Furthermore, TE-CSA is associated with comorbid conditions that benefit from identification and treatment (e.g., atrial fibrillation). Thus recognition, appreciation of the natural history, and initiation of targeted management for TE-CSA may improve the control of sleep-disordered breathing (SDB), patient's symptoms, and quality of life.

Pathophysiology

Because specific studies on TE-CSA pathophysiology are lacking, understanding of this disorder relies on investigations in other central sleep apnea syndromes.

The pathophysiology of TE-CSA reflects a disordered interplay between (1) upper airway (UA) collapsibility, (2) ventilatory system instability, and (3) a propensity for arousals. Central sleep apnea or periodic breathing is primarily a manifestation of instability of the ventilatory system, coordinated by a feedback loop between the chemo- (and other) receptors, the respiratory controller, and the pump (airways, lungs, muscles) [5]. Ventilatory instability can be measured by a system's loop gain and a CO_2 reserve. Loop gain is considered high when the respiratory center's sensitivity to changes in arterial partial pressure of CO_2 ($PaCO_2$) or arterial partial pressure of O_2 (PaO_2) (i.e., controller gain) is high, or when the lungs have increased efficiency of CO_2 excretion (i.e., plant gain). CO_2 reserve is defined as the difference between $PaCO_2$ at eupnea (stable breathing) and $PaCO_2$ at apnea (the apneic threshold). When ventilatory response is exuberant (high loop gain), $PaCO_2$ decreases below the apneic threshold, and central apneas ensue. These events can be further exacerbated by easy arousability and sleep state instability [6, 7]. Because eupneic $PaCO_2$ in sleep is normally 3–5 mmHg higher than that during wakefulness, with awakening the nocturnal eupneic $PaCO_2$ is "perceived" by the respiratory centers as hypercapnic. The resultant increase in ventilatory drive combined with removal of UA resistance of sleep leads to hyperventilation with increased propensity for central apneas and periodic breathing [5–7].

On diagnostic polysomnography, patients with TE-CSA exhibit a pattern that includes airway obstruction, mixed apneas, and periodic breathing in NREM sleep with resolution of above or occurrence of more "pure" obstructive events during REM. Features helpful in recognition of both relatively pure obstructive and elevated loop gain/low CO_2 reserve events are noted in Table 8.1.

In TE-CSA, the relief of UA obstruction provided by CPAP, oral appliance, or tracheostomy is believed to reveal an elevated loop gain leading to hypocapnia with central apneas and short-cycle periodic breathing, similar to respiration at high

Table 8.1 Recognition of various forms of sleep apnea

Polysomnographic feature	Relatively pure obstructive sleep apnea	High loop gain sleep apnea
Periodic breathing, Cheyne-Stokes	Rare	Typical (often short cycle, <30 s in absence of CHF)
Respiratory event timing	Variable (each event tends to have different durations)	Self-similar/metronomic
Severity during sleep state	Greater severity in REM	Minimal severity in REM
Effort signal morphology	Well maintained during obstructed breath	Complete or partial loss between recovery breaths
Flow-effort relationship	Discordant: flow is reduced disproportionately to reduction in effort	Concordant: flow and effort follow each other in amplitude
Arousal timing	Early part of event termination	Crests event, often in the center of the sequence of recovery breaths
Oxygen desaturation	Irregular, progressive drops, V-shaped contour	Smooth, symmetric, progressive drops rare

CHF Congestive heart failure, *REM* rapid eye movement

altitude [8]. In addition to conditions and processes predisposing to CSA in general, OSA severity may play a role in raising loop gain, as TE-CSA is higher among patients with severe versus mild OSA. Additional proposed contributors to TE-CSA include CO_2 washout (i.e., anatomical dead-space reduction) with effective CPAP or leak [9] and overactivation of lung stretch receptors with CPAP therapy (particularly at higher pressures) [10]. The role of the CO_2 control instability and hypocapnia in pathogenesis of TE-CSA is supported by resolution with small increases of inhaled CO_2 [11]. Stabilizing respiratory motor output by preventing transient hypocapnia with isocapnic rebreathing also prevents most of the OSA in patients with unstable ventilatory control (high loop gain, low CO_2 reserve) and collapsible airway.

Diagnosis, Epidemiology, and Natural History

In the International Classification of Sleep Disorders – Third Edition (ICSD-3), TE-CSA is defined as five or more central apneas or hypopneas per hour of sleep (CAHI ≥5/h), with central events making up ≥50% of all respiratory events during titration of PAP without a back-up rate [12]. The central apneas or periodic breathing should not be better explained by another disorder, such as CSA with Cheyne-Stokes breathing (CSB) or CSA associated with opioid use. Alternative definitions

of TE-CSA, previously known as "complex sleep apnea," have varied in criteria such as presence of periodic breathing and inclusion of comorbid disorders (e.g., congestive heart failure, opioid use) [13–16]. While these various definitions all aim to capture the concept of increased propensity for CSA in the setting of resolution of UA obstruction, this variability has contributed to a wide range of estimates of TE-CSA prevalence and natural history.

The prevalence of TE-CSA ranges between 0.6% and 20% and is based primarily on retrospective studies [3, 16]. It is higher in studies using split-night polysomnograms (likely reflecting a higher severity SDB) and patients with cardiac comorbidities such as heart failure (HF) [16]. In the largest prospective study ($n = 675$) by Cassel et al. [13], the prevalence was 12% at 3-month follow-up, when defined as CAI ≥5/h or predominant periodic breathing pattern on effective CPAP (OAHI <5/h).

Importantly, there are three trajectories of TE-CSA: resolution, persistence, and late emergence [17]. Cassel et al. found that among those who had TE-CSA on initial titration or at 3-month follow-up, it resolved in 57%, persisted in 20%, and emerged during 3 months in 23% [13]. These findings are remarkably similar to a recent retrospective analysis of US PAP telemonitoring data in 133,000 patients of which 3.5% were found to have CAI ≥5/h at baseline [3]. Resolution occurred in 55%, persistence in 25%, and late emergence in 20%.

TE-CSA is thus a dynamic process, and evaluation at a single point in time (e.g., titration study) is likely to miss a significant number of patients. This is relevant because patients with TE-CSA are at higher risk of discontinuing CPAP, and targeting treatment modality (e.g., ASV) can improve residual respiratory event burden, adherence, and sleep quality [3, 4, 18]. Thus ongoing monitoring (including interrogation of PAP device data) and use of features capturing elevated loop gain and arousability can help identify those who could benefit from treatment.

Clinical Presentation and Evaluation

History

Similar to our patient, patients with TE-CSA present with a combination of the symptoms found in patients with "classic" OSA and CSA, including sleepiness, insomnia, poor sleep quality, fatigue, and neurocognitive complaints. Given the dynamic nature of TE-CSA, longitudinal assessments of sleepiness (e.g., Epworth sleepiness scale) and sleep disturbance (e.g., insomnia severity scale) are prudent. Increasing age and lower body mass index (BMI) have been reported as risk factors for TE-CSA (in comparison to "relatively pure" OSA) [16]. Examination findings may be consistent with those of associated disorders.

Associated Conditions

Patients with TE-CSA on polysomnography commonly exhibit hypertension, coronary artery disease, atrial fibrillation, and HF [19, 20]. Chronic opioid use is associated with TE-CSA [15], and its withdrawal can reverse TE-CSA [21]. Notably, up to 30% of patients present without recognizable comorbidities [19].

Polysomnographic Features

The most characteristic feature of TE-CSA is NREM dominance of respiratory events and sleep fragmentation, with treatment-emergent events occurring almost exclusively in non-slow-wave NREM sleep as noted for our patient (Fig. 8.2). The most consistent predictors of TE-CSA on a diagnostic portion of the study are a high AHI (usually ≥30/h) and an elevated CAI ≥5/h, while REM predominance of respiratory events is a negative predictor [16, 22], likely due to decreased chemosensitivity during REM. Additional features suggestive of TE-CSA include periodic breathing with obstruction that resolves or improves in REM sleep (Fig. 8.4) as well those noted in Table 8.1 [5].

Both under- and over-titration, as well as excess leak [9], can lead to central events and thus should be addressed prior to diagnosis of TE-CSA. Absolute CPAP do not consistently predict occurrence, while bilevel PAP (BPAP), likely due to higher propensity to induce hypocapnia, is a common risk factor [17, 22].

Identifying patients at risk for persistent or delayed TE-CSA might help select those benefiting from non-CPAP therapy early. Unfortunately, other than higher CAI (usually ≥5/h) on a diagnostic portion of the study, no other predictors are consistent [13, 15, 17, 23]. A pilot study found that those with higher loop gain (>2), as measured by the duty ratio (duration of ventilation divided by cycle duration [sum of ventilatory and apneic phases] of CSA) during stable NREM sleep at optimal CPAP (OAHI <5/h), predicted lack of response to CPAP at 1 month [24].

Home Sleep Apnea Testing (HSAT) and PAP Data

While there are no studies of TE-CSA involving HSAT, clinical experience suggests that those with TE-CSA might be recognized by elevated CAI and periodic breathing that may manifest as “zipper-like” oxygen desaturations on HSAT, as opposed to the deeper, more irregular, and possibly V-shaped desaturations (i.e., REM-related) encountered in predominant OSA pattern (Fig. 8.5). Such characteristics may warrant an in-lab titration rather than auto-PAP initiation. TE-CSA may be identified on review of CPAP data. In a study by Liu et al., the mean machine-derived AHI and CAI were >15/h and >10/h, respectively, in the first 10 days of CPAP treatment in the persistent TE-CSA group and remained consistently higher than AHI and CAI in patients with standard OSA, transient TE-CSA, and delayed TE-CSA [3].

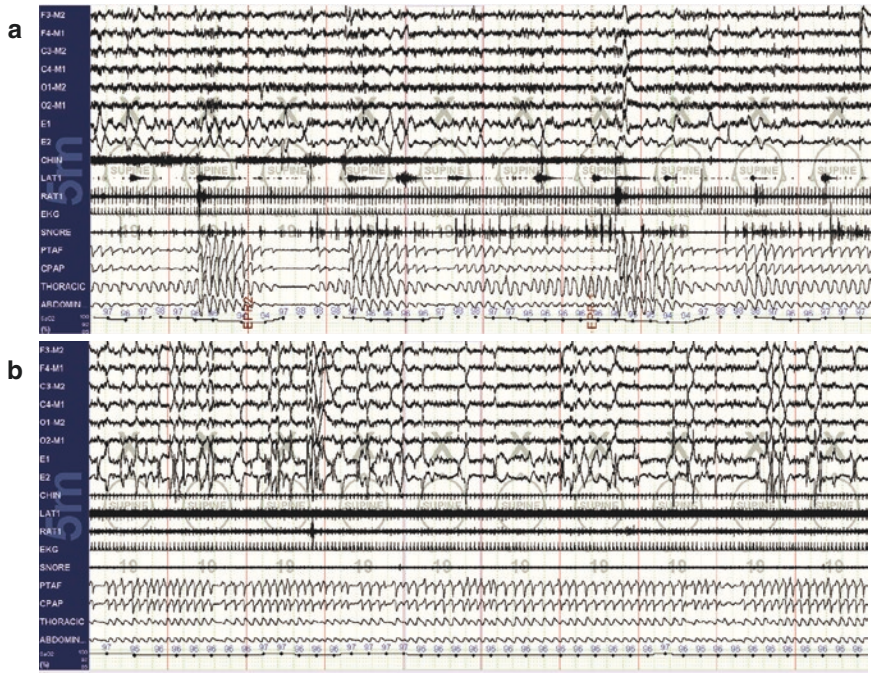


Fig. 8.4 (**a**) NREM-dominant sleep apnea, with continuous positive airway pressure (CPAP) during NREM sleep. Five-minute screen compression; each vertical line is 30 s. Unresolved respiratory events occur across a range of CPAP (5–19 cm) with long cycle events, some periodic breathing features, and clear obstructive features. (**b**) NREM-dominant sleep apnea during REM sleep. Spontaneous transition to REM sleep showing resolution of all abnormality (Adapted from Zinchuk A, Thomas, R. Central Sleep Apnea: Diagnosis and Management in Principles and Practice of Sleep Medicine, 2016, with permission)

Assessments of Physiologic Contributors to TE-CSA

Standard tools to assess UA collapsibility, compensation, loop gain, and arousability are still confined to few research centers with specialized signal processing capabilities [25]. Clinical titration polysomnograms can be used to estimate loop gain using the duty ratio as described above [24]. Hypocapnia can be assessed by transcutaneous or mainstream end-tidal CO_2. Low arousal threshold can be predicted from diagnostic portion of polysomnography in patients who exhibit two of the following: AHI <30/h, fraction of hypopneas >0.58, and oxygen saturation nadir >82.5% [26]. While none of these have been prospectively tested to target specific therapies in TE-CSA, they provide a roadmap for complementary approaches in cases similar to our patient, where established treatments do not effectively eliminate SDB.

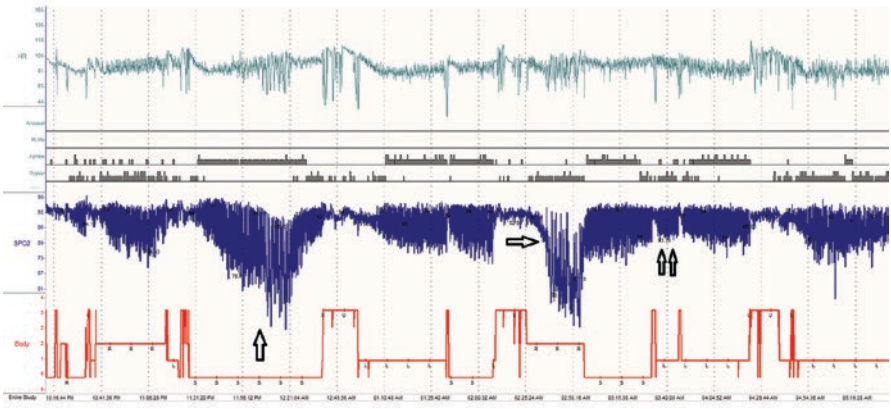


Fig. 8.5 Manifestation of different desaturation patterns on home sleep study. Single arrows represent irregular, progressive, and sometimes V-shaped contour desaturations often associated with rapid eye movement (REM) sleep and obstructive events. Double arrows highlight more smooth, symmetric, and "zipper" desaturation pattern indicative of high loop gain sleep apnea often associated with periodic breathing and central apneas

Treatment

There are no consensus guidelines for management of TE-CSA. Although majority of patients improve with expectant CPAP treatment, TE-CSA confers a greater risk of CPAP non-adherence and therapy termination [3, 27], suggesting that early tailored treatment (e.g., ASV, CPAP, or ASV with adjunctive therapies) may be appropriate. Whether such a strategy prospectively improves symptoms and quality of life and is cost-effective needs validation.

Our approach (Fig. 8.6) includes phenotyping when possible and a patient-centered discussion about goals of treatment, TE-CSA trajectories, and the risks and benefits of expectant or early tailored treatment approaches. We have found close monitoring of symptoms, PAP data downloads, and, if indicated, repeat titration polysomnography to be key for successful treatment.

Conservative Measures

Since TE-CSA can occur from under- or over-titration of PAP therapy, excess leak, and positional influences, we ensure adequacy of titration and mask fit and evaluate for effect of positional therapy. If indicated, weight loss and good sleep hygiene practices should be advised. Assessment and optimal control of the underlying condition is recommended, such as guideline-based HF treatment. For patients on opioid therapy, dose reduction or exploration of non-opioid analgesia should be sought as reduction can improve or alleviate CSA [15, 21].

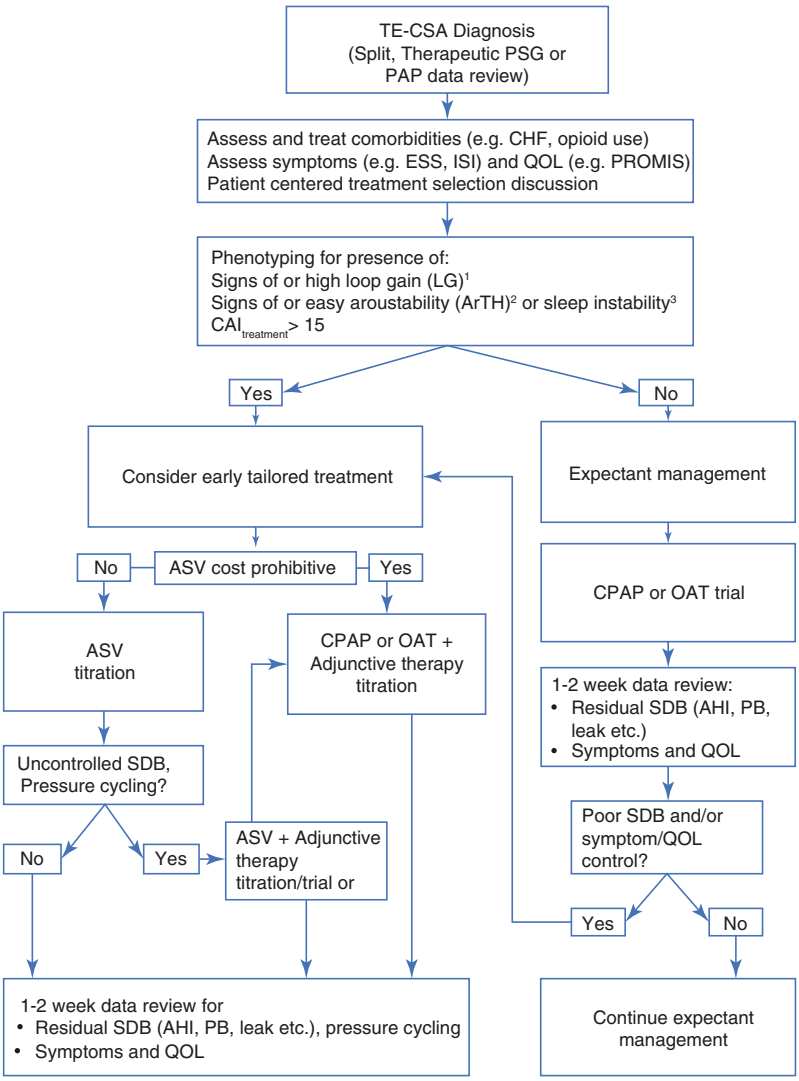


Fig. 8.6 One approach to management of TE-CSA. Adjunctive therapy targeting *high loop gain (LG)* includes acetazolamide, O_2, non-vented mask, enhanced expiratory rebreathing space; Adjunctive therapy targeting *low arousal threshold (ArTH) or fragmented sleep* includes sedative hypnotics. All patients attempt positional therapy if positional predominance is noted. [1]LG > 2 as measured by Stanchina et al. [24], periodic breathing >30% of treatment study, hypocapnia on CO_2 monitoring. [2]Low ArTH as measured by Edwards et al. [26]. [3]Sleep instability, as suggested by prolonged sleep-wake transitional instability (>10 min), low sleep efficiency (<70%), high N1 stage during PAP titration (>15%), and poor evolution of slow wave sleep (<1 Hz). AHI, Apnea hypopnea index; ASV, adaptive servo-ventilation; CAI, central apnea index; CHF, congestive heart failure; ESS, Epworth sleepiness scale; ISI, insomnia severity scale; PROMIS, Patient-Reported Outcomes Measurement Information System Sleep Disturbance; QOL, quality of life; OAT, oral appliance therapy; PAP, positive airway pressure; PB, periodic breathing; SDB, sleep-disordered breathing; TE-CSA, treatment-emergent central sleep apnea

PAP Therapies

1. Continuous and bilevel PAP

Expectant management with UA stabilization by CPAP or oral appliance is supported by findings that ventilatory control instability can improve with time [28]. Unfortunately, this was not the case for our patient, and may be more likely in those with a picture similar to "classic" OSA such as REM predominance, and lower CAIs and improved sleep efficiency on titration, as well as in those without comorbid HF or opioid use [20].

BPAP without back-up rate is not recommended because increased ventilation exaggerates central apneas and periodic breathing [18]. BPAP with back-up rate can reduce CSA as machine-delivered mandatory breaths substitute for lack of patient-derived effort, but re-emergence of CSA occurs, and other modes of ventilation (e.g., ASV) are more effective over time.

If expectant management approach is selected, it is critical to monitor symptoms and PAP data to determine patient trajectory and symptoms. TE-CSA may persist on CPAP despite improvement in sleepiness [15, 19]; thus monitoring of other sleep disturbance symptoms (e.g., insomnia) is prudent.

2. Adaptive servo-ventilation (ASV)

ASV devices are primarily designed for elevated loop gain and hypocapnic CSA, as in patients with HF and CSB. All ASVs provide expiratory support, inspiratory pressure support, and back-up rates guided by measures of ventilation or flow averaged over 3–4 min. Details of ASV operation and titration strategies can be obtained from recent comprehensive reviews [29, 30]. Retrospective studies and small clinical trials show that in TE-CSA, ASV improves the AHI, desaturations, respiratory-related arousals, and REM sleep and does so better than CPAP or BPAP with back-up rate [4, 18, 31, 32]. In a randomized cross-over trial of nine patients with TE-CSA, the residual AHI (CAI) on ASV was markedly lower compared to CPAP in the acute setting (2 ± 4/h (0 ± 0/h) vs. 42 ± 28/h (31 ± 19/h), respectively) [33]. This advantage tends to wane over time likely due to the resolution of TE-CSA in some. In a clinical trial involving 66 TE-CSA patients randomized to ASV vs. CPAP for 90 days, the residual AHI (CAI) at follow-up was 4 ± 10/h (1 ± 3/h) vs. 10 ± 11/h, (5 ± 6/h), respectively [32]. The primary outcome (AHI <10/h) was achieved in 90% of participants on ASV vs. 65% of those on CPAP (p-value 0.02). Whether this advantage translates to long-term improvements in daytime symptoms and quality of life needs to be evaluated. ASV is generally better tolerated than CPAP by TE-CSA patients, and retrospective studies suggest that switching from CPAP to ASV improves both residual respiratory events and adherence [4, 18].

In TE-CSA patients with heart failure (both systolic and diastolic), ASV improves central apneas as well as neurohormonal and cardiac function parameters [34, 35]. However, its use in patients with CSA associated with symptomatic HF and reduced ejection fraction (<45%), including TE-CSA, should be avoided due to an absolute 6% increase in all-cause and cardiovascular mortality found in a recent trial [36].

As with our patient, a subset of patients may demonstrate immediate ASV intolerance and desynchrony effects that do not appear to resolve with time. A phenomenon called "pressure cycling," or high variability of pressure support (Fig. 8.3), highlights the importance of assessing ASV efficacy using a ventilator pressure output signal rather than simply the flow or effort signal. Pressure cycling is a response of ASV to ongoing pathologic periodic breathing. Persistent pressure cycling can lead to sleep fragmentation and blood pressure elevations, even if respiration as measured by flow is "improved" [37]. Such findings may warrant use of targeted adjunctive, non-PAP therapies.

Non-PAP Therapies

1. Oxygen

Oxygen lowers loop gain and widens CO_2 reserve and thus reduces AHI in patients with CHF and CSA-CSB [38]. Adding O_2 to PAP may be of benefit for TE-CSA patients, as shown in a retrospective analysis that found a lower AHI in patients treated with CPAP and O_2 vs. CPAP alone [18]. Drawbacks to O_2 use include increase in respiratory event duration and negation of desaturations in scoring of hypopneas, which may "reduce" the AHI but not imply stabilization of disease.

2. Minimizing hypocapnia

Minimizing hypocapnia may stabilize breathing in TE-CSA. OSA patients with high loop gain and small CO_2 reserve might be best candidates [39]. One way to maintain P_aCO_2 above the apneic threshold is to use dead-space rebreathing. In CSA-CSB patients with HF, rebreathing has demonstrated improvements in apneas and arousals [40]. A retrospective case series of 204 patients with "CPAP-refractory" CSA showed that addition of an "enhanced expiratory rebreathing space" (EERS) with 50–150 mL of tubing and a non-vented mask added to PAP therapy markedly improved AHI and sleep efficiency [8]. In this study, EERS was not administered to subjects with $ET_{CO2} > 45$ mmHg, and there was an average increase in ET_{CO2} from 38 ± 3 to 39 ± 3 mmHg, similar to that observed in our patient's case. However, among CSA-CSB patients with HF, there are reports of increased sleep fragmentation with dead space and concerns about sympathetic activation [41]. Long-term effects of added dead space are unknown. If this approach is used, measurement of CO_2 to assess for hypocapnia at baseline and CO_2 changes with treatment is mandatory, along with an evaluation of the effects on sleep architecture and symptoms.

3. Carbonic anhydrase inhibition

Acetazolamide, a carbonic anhydrase inhibitor, is a respiratory stimulant. It improves ventilatory instability by reducing loop gain (acidosis driven reduction of CO_2 clearance and widening of CO_2 reserve) [42]. Small short-term studies show

that it significantly reduces the AHI in CSA [43] and OSA with elevated loop gain [42], but residual events remain. Thus, acetazolamide is likely to be most efficacious in conjunction with UA stabilization. In a randomized study of OSA patients using auto-PAP who develop CSA at high altitude (pathophysiology similar to TE-CSA), acetazolamide reduced the AHI and improved time spent at O_2 saturations below 90% [44]. In the longest randomized trial among unselected OSA patients comparing 250 mg of acetazolamide three times daily with CPAP vs. CPAP or acetazolamide alone, the combination therapy exhibited most pronounced improvement of SDB [45]. If used, best candidates might be patients with elevated loop gain [42], and anecdotal experience suggests that doses as low as 125 mg may be effective. Most common adverse effects are paresthesia, dyspepsia, diarrhea, and nocturia, but it is generally well tolerated and patients tend not to discontinue treatment [45]. Due to induction of acidosis, caution in renal disease is warranted, as is monitoring for hypovolemia and hypokalemia.

4. Sedative hypnotics

Easy arousability from sleep can worsen CSA, by means of hyperpnea and ventilatory overshoot, and OSA, by not allowing sufficient time to recruit UA muscles. Sedative hypnotics have been used to improve CSA (zolpidem) [46] and OSA (eszopiclone) [47] with low arousal threshold. Putative mechanisms include reduction in arousal-induced hypocapnia and increasing proportion of NREM sleep in stable breathing. Sedative hypnotics are unlikely to be a successful sole therapy in TE-CSA as they can unmask obstruction in CSA and prolong apnea duration in some with OSA. In the longest trial in unselected 160 OSA patients, eszopiclone facilitated improvement in CPAP titrations with fewer residual events and fewer incomplete titrations [48]. However, these findings are not universal [49]. Estimation of low arousal threshold may be helpful in selecting candidates [26, 47]. Caution should be used in the elderly, those at risk of falls, those using other sedatives or alcohol or opioids, and in those with hypoventilation.

Clinical Pearls

- Treatment-emergent central sleep apnea (TE-CSA) is a syndrome that presents as obstructive sleep apnea (OSA) during a diagnostic portion of a sleep testing followed by an “unmasking” of a central sleep apnea (CSA) as obstruction is alleviated.
- TE-CSA is a non-rapid eye movement (NREM) predominant process, and improvement in REM is characteristic.
- Putative mechanisms include an overly sensitive ventilatory system (increased loop gain with narrow CO_2 reserve) and sleep-wake state instability.

- According to the International Classification of Sleep Disorders – Third Edition (ICSD-3), diagnosis is based on central apnea hypopnea index (CAHI) ≥5/h and ≥50% of total respiratory events being central while on continuous positive airway pressure (CPAP) therapy. Some patients may be missed with this approach given the underscoring of central hypopneas.
- Because central events can occur due to mask leak, inadequate or overly aggressive CPAP titration should be ruled out prior to diagnosis of TE-CSA.
- Roughly 5–10% of OSA patients manifest TE-CSA.
- TE-CSA is associated with conditions that predispose to CSA including heart failure, atrial fibrillation, and opioid use. However, a third of patients have no comorbidities.
- TE-CSA trajectories vary, with resolution occurring in about 50%, persistence in 25%, and late development (weeks after therapy initiation) in another 25% at 3 months.
- No reliable predictors of TE-CSA trajectories exist, and the optimal treatment approach is not known.
- Since TE-CSA resolves in a majority, close observation on CPAP may be attempted. However, TE-CSA is associated with poor adherence and CPAP use termination, which can be addressed with early tailored therapies such as adaptive servo-ventilation (ASV) and/or adjunctive therapies (e.g., dead space, hypnotics).
- ASV is a first-line treatment for TE-CSA if observation on CPAP is not tried. It is superior to CPAP in improving the AHI; however, the evidence on long-term symptoms, quality of life, and other outcomes is lacking. ASV in patients with heart failure and reduced ejection fraction is contraindicated given the association with increased mortality.
- Pressure cycling is a phenomenon of pressure support variability associated with ongoing periodic breathing, sleep fragmentation, and blood pressure elevation while on ASV. Therefore, ASV efficacy should be evaluated using the ventilator pressure output, because flow or machine residual AHI can give a false sense of "success."
- Because of multifactorial nature of TE-CSA pathogenesis, optimal treatment likely involves multi-modality therapy targeting ventilatory and sleep state instability.
- Assessing loop gain and arousal threshold from clinical data may help identify patients for adjunctive therapies; however, validation of this approach is needed. Adjunctive treatments include minimizing hypocapnia via non-ventilated masks, added dead space, oxygen, carbonic anhydrase inhibitors, and sedative hypnotics.

References

1. Malhotra A, Bertisch S, Wellman A. Complex sleep apnea: it isn't really a disease. J Clin Sleep Med. 2008;4:406–8.
2. Morgenthaler TI, Kagramanov V, Hanak V, Decker PA. Complex sleep apnea syndrome: is it a unique clinical syndrome? Sleep. 2006;29:1203–9.
3. Liu D, Armitstead J, Benjafield A, et al. Trajectories of emergent central sleep apnea during CPAP therapy. Chest. 2017;152:751–60.
4. Pepin JD, Woehrle H, Liu D, et al. Adherence to positive airway therapy after switching from CPAP to ASV: a big data analysis. J Clin Sleep Med. 2018;14:57–63.
5. Zinchuk A, Thomas R. Central sleep apnea: diagnosis and management. In: Kryger M, Roth T, Dement WC, editors. Principles and practice of sleep medicine. 6th ed. Philadelphia: Elsevier; 2017.
6. Dunai J, Kleiman J, Trinder J. Ventilatory instability during sleep onset in individuals with high peripheral chemosensitivity. J Appl Physiol. 1999;87:661–72.
7. Eckert DJ, Younes MK. Arousal from sleep: implications for obstructive sleep apnea pathogenesis and treatment. J Appl Physiol. 2014;116:302–13.
8. Gilmartin G, McGeehan B, Weiss JW, Thomas RJ. Treatment of positive airway pressure treatment-associated respiratory instability with enhanced expiratory rebreathing space (EERS). J Clin Sleep Med. 2010;6:529–38.
9. Montesi SB, Bakker JP, Macdonald M, et al. Air leak during CPAP titration as a risk factor for central apnea. J Clin Sleep Med. 2013;9:1187–91.
10. Hoffman M, Schulman DA. The appearance of central sleep apnea after treatment of obstructive sleep apnea. Chest. 2012;142:517–22.
11. Thomas RJ, Daly RW, Weiss JW. Low-concentration carbon dioxide is an effective adjunct to positive airway pressure in the treatment of refractory mixed central and obstructive sleep-disordered breathing. Sleep. 2005;28:69–77.
12. American Academy of Sleep Medicine. International classification of sleep disorders. Darien: American Academy of Sleep Medicine; 2014.
13. Cassel W, Canisius S, Becker HF, et al. A prospective polysomnographic study on the evolution of complex sleep apnoea. Eur Respir J. 2011;38:329–37.
14. Javaheri S, Harris N, Howard J, Chung E. Adaptive servoventilation for treatment of opioid-associated central sleep apnea. J Clin Sleep Med. 2014;10:637–43.
15. Javaheri S, Smith J, Chung E. The prevalence and natural history of complex sleep apnea. J Clin Sleep Med. 2009;5:205–11.
16. Nigam G, Pathak C, Riaz M. A systematic review on prevalence and risk factors associated with treatment- emergent central sleep apnea. Ann Thorac Med. 2016;11:202–10.
17. Nigam G, Riaz M, Chang ET, Camacho M. Natural history of treatment-emergent central sleep apnea on positive airway pressure: a systematic review. Ann Thorac Med. 2018;13:86–91.
18. Allam JS, Olson EJ, Gay PC, Morgenthaler TI. Efficacy of adaptive servoventilation in treatment of complex and central sleep apnea syndromes. Chest. 2007;132:1839–46.
19. Kuzniar TJ, Kasibowska-Kuzniar K, Ray DW, Freedom T. Clinical heterogeneity of patients with complex sleep apnea syndrome. Sleep Breath. 2013;17:1209–14.
20. Kuzniar TJ, Morgenthaler TI. Treatment of complex sleep apnea syndrome. Chest. 2012;142:1049–57.
21. Schwarzer A, Aichinger-Hinterhofer M, Maier C, Vollert J, Walther JW. Sleep-disordered breathing decreases after opioid withdrawal: results of a prospective controlled trial. Pain. 2015;156:2167–74.
22. Moro M, Gannon K, Lovell K, Merlino M, Mojica J, Bianchi MT. Clinical predictors of central sleep apnea evoked by positive airway pressure titration. Nat Sci Sleep. 2016;8:259–66.
23. Reiter J, Zleik B, Bazalakova M, Mehta P, Thomas RJ. Residual events during use of CPAP: prevalence, predictors, and detection accuracy. J Clin Sleep Med. 2016;12:1153–8.

24. Stanchina M, Robinson K, Corrao W, Donat W, Sands S, Malhotra A. Clinical use of loop gain measures to determine continuous positive airway pressure efficacy in patients with complex sleep apnea. A pilot study. Ann Am Thorac Soc. 2015;12:1351–7.
25. Sands SA, Edwards BA, Terrill PI, et al. Phenotyping pharyngeal pathophysiology using polysomnography in patients with obstructive sleep apnea. Am J Respir Crit Care Med. 2018;197:1187–97.
26. Edwards BA, Eckert DJ, McSharry DG, et al. Clinical predictors of the respiratory arousal threshold in patients with obstructive sleep apnea. Am J Respir Crit Care Med. 2014;190:1293–300.
27. Pusalavidyasagar SS, Olson EJ, Gay PC, Morgenthaler TI. Treatment of complex sleep apnea syndrome: a retrospective comparative review. Sleep Med. 2006;7:474–9.
28. Salloum A, Rowley JA, Mateika JH, Chowdhuri S, Omran Q, Badr MS. Increased propensity for central apnea in patients with obstructive sleep apnea: effect of nasal continuous positive airway pressure. Am J Respir Crit Care Med. 2010;181:189–93.
29. Javaheri S, Brown LK, Randerath WJ. Clinical applications of adaptive servoventilation devices: part 2. Chest. 2014;146:858–68.
30. Javaheri S, Brown LK, Randerath WJ. Positive airway pressure therapy with adaptive servoventilation: part 1: operational algorithms. Chest. 2014;146:514–23.
31. Dellweg D, Kerl J, Hoehn E, Wenzel M, Koehler D. Randomized controlled trial of noninvasive positive pressure ventilation (NPPV) versus servoventilation in patients with CPAP-induced central sleep apnea (complex sleep apnea). Sleep. 2013;36:1163–71.
32. Morgenthaler TI, Kuzniar TJ, Wolfe LF, Willes L, McLain WC 3rd, Goldberg R. The complex sleep apnea resolution study: a prospective randomized controlled trial of continuous positive airway pressure versus adaptive servoventilation therapy. Sleep. 2014;37:927–34.
33. 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.
34. Bitter T, Westerheide N, Hossain MS, et al. Complex sleep apnoea in congestive heart failure. Thorax. 2011;66:402–7.
35. Heider K, Arzt M, Lerzer C, et al. Adaptive servo-ventilation and sleep quality in treatment emergent central sleep apnea and central sleep apnea in patients with heart disease and preserved ejection fraction. Clin Res Cardiol. 2018;107:421–9.
36. Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. N Engl J Med. 2015;373:1095–105.
37. Gunn S, Naik S, Bianchi MT, Thomas RJ. Estimation of adaptive ventilation success and failure using polysomnogram and outpatient therapy biomarkers. Sleep. 2018;41:zsy033; e-pub Feb 23.
38. Sakakibara M, Sakata Y, Usui K, et al. Effectiveness of short-term treatment with nocturnal oxygen therapy for central sleep apnea in patients with congestive heart failure. J Cardiol. 2005;46:53–61.
39. Xie A, Teodorescu M, Pegelow DF, et al. Effects of stabilizing or increasing respiratory motor outputs on obstructive sleep apnea. J Appl Physiol. 2013;115:22–33.
40. Khayat RN, Xie A, Patel AK, Kaminski A, Skatrud JB. Cardiorespiratory effects of added dead space in patients with heart failure and central sleep apnea. Chest. 2003;123:1551–60.
41. Andreas S, Weidel K, Hagenah G, Heindl S. Treatment of Cheyne-Stokes respiration with nasal oxygen and carbon dioxide. Eur Respir J. 1998;12:414–9.
42. Edwards BA, Sands SA, Eckert DJ, et al. Acetazolamide improves loop gain but not the other physiological traits causing obstructive sleep apnoea. J Physiol. 2012;590:1199–211.
43. Javaheri S. Acetazolamide improves central sleep apnea in heart failure: a double-blind, prospective study. Am J Respir Crit Care Med. 2006;173:234–7.
44. Latshang TD, Nussbaumer-Ochsner Y, Henn RM, et al. Effect of acetazolamide and autoCPAP therapy on breathing disturbances among patients with obstructive sleep apnea syndrome who travel to altitude: a randomized controlled trial. JAMA. 2012;308:2390–8.

45. Eskandari D, Zou D, Grote L, Hoff E, Hedner J. Acetazolamide reduces blood pressure and sleep-disordered breathing in patients with hypertension and obstructive sleep apnea: a randomized controlled trial. J Clin Sleep Med. 2018;14:309–17.
46. Quadri S, Drake C, Hudgel DW. Improvement of idiopathic central sleep apnea with zolpidem. J Clin Sleep Med. 2009;5:122–9.
47. Eckert DJ, Owens RL, Kehlmann GB, et al. Eszopiclone increases the respiratory arousal threshold and lowers the apnoea/hypopnoea index in obstructive sleep apnoea patients with a low arousal threshold. Clin Sci (Lond). 2011;120:505–14.
48. Lettieri CJ, Quast TN, Eliasson AH, Andrada T. Eszopiclone improves overnight polysomnography and continuous positive airway pressure titration: a prospective, randomized, placebo-controlled trial. Sleep. 2008;31:1310–6.
49. Park JG, Olson EJ, Morgenthaler TI. Impact of zaleplon on continuous positive airway pressure therapy compliance. J Clin Sleep Med. 2013;9:439–44.

Chapter 9
Upper Airway Resistance Syndrome

Robert Hiensch and David M. Rapoport

Abbreviations

AASM	American Academy of Sleep Medicine
AHI	Apnea-hypopnea index
CPAP	Continuous positive airway pressure
EEG	Electroencephalogram
ESS	Epworth Sleepiness Scale
ICSD-3	International Classification of Sleep Disorders – Third Edition
IFL	Inspiratory flow limitation
MAD	Mandibular advancement device
NC/PT	Nasal cannula/pressure transducer
OCST	Out-of-center sleep test
OSA	Obstructive sleep apnea
Pcrit	Pharyngeal critical pressure
PSG	Polysomnography
REM	Rapid eye movement
RERA	Respiratory effort-related arousal
UARS	Upper airway resistance syndrome

R. Hiensch (✉) · D. M. Rapoport
Icahn School of Medicine at Mount Sinai, Mount Sinai Hospital, Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, New York, NY, USA

C. Won (ed.), *Complex Sleep Breathing Disorders*,
https://doi.org/10.1007/978-3-030-57942-5_9

Case

DL is a 45-year-old woman with a past medical history of anxiety and hyperlipidemia who was referred by her primary care physician for evaluation of sleep maintenance insomnia. Her symptoms started about 4 years ago but have progressively worsened over the last year. She generally feels fatigued at night and gets into bed around 10:30 PM. Her estimated sleep latency is usually less than 30 min, although lately it has been longer several times per week. She reports several arousals throughout the night and often has difficulty falling back into a "deep sleep." Her husband reports that she snores but he is not aware of any pauses in her breathing (apneas). Her alarm is set for 6:30 AM although she is usually awake by the time it goes off. She generally feels unrefreshed in the morning. She denies waking up with a dry mouth unless she has a cold. She endorses headaches, but they can occur throughout the day. She drinks one coffee in the morning and one in the afternoon. She feels fatigued during most of the day, yet has difficulty taking naps, even when she has the opportunity to do so. She denies symptoms of restless leg syndrome, parasomnias, cataplexy, and bruxism.

She had been previously given a trial of zolpidem 5 mg at night to be taken half an hour before bedtime. Her symptoms did not improve. She was then tried on a low dose of eszopiclone but she continued to experience arousals, although she thinks she was able to return to sleep more quickly with this medication. Her daytime symptoms did not improve significantly, however. She has taken measures to improve her sleep hygiene: she keeps a regular sleep schedule, avoids electronics at night including her cell phone, and has joined a morning exercise class. She also does not stay in bed for prolonged periods of time when she does wake up in the middle of the night.

She denies any history of cardiac dysrhythmias, hypertension, stroke, and type 2 diabetes mellitus. She has had no prior surgeries. Her review of systems is positive for frequent gastrointestinal complaints, including alternating diarrhea and constipation. She endorses seasonal allergies. Her current medications include 5 mg of rosuvastatin and lorazepam 1 mg as needed, which she takes infrequently. She denies any drug allergies. She is a never smoker. She uses alcohol occasionally at night to relax but limits herself to one drink at most. She denies any illicit drug use. She works at an advertisement agency.

Physical exam reveals normal vital signs. Her body mass index (BMI) is 24 kg/m^2. She is in no distress but is mildly anxious. Examination of the head and neck reveals a mildly deviated nasal septum with increased nasal resistance on the affected side. There is no turbinate hypertrophy. She has a vaulted palate with crowded molar teeth. She has a slight overjet and mild micrognathia. There is no tongue scalloping. Her posterior oropharynx is narrow. Her Mallampati Score is 2. Tonsils are grade 1 and normal in appearance. Her uvula is midline and somewhat elongated. Her neck is supple without any goiters or lymphadenopathy. The rest of her exam is normal.

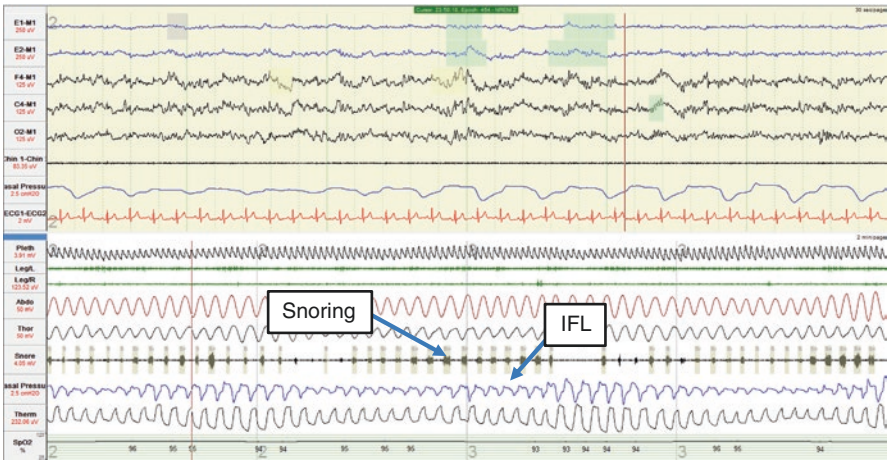


Fig. 9.1 Representative epoch from the case presentation demonstrates prolonged periods of inspiratory flow limitation on the nasal cannula/pressure transducer (blue tracing) accompanied by snoring. EEG shows alpha-frequency intrusion into sleep

She scores 8 out of 24 on the Epworth Sleepiness Scale (ESS). Review of performed laboratory work reveals a normal hemoglobin value, serum bicarbonate value, ferritin level, and thyroid-stimulating hormone.

A nocturnal polysomnography (PSG) was ordered. The test demonstrates prolonged periods of inspiratory flow limitation as manifested by a flattening of the inspiratory limb of airflow as detected by a nasal cannula/pressure transducer (NC/PT) (Fig. 9.1). There were frequent arousals from sleep and alpha-frequency intrusion during delta sleep was noted. The apnea-hypopnea index (AHI) using the recommended criteria of a ≥30% peak signal excursion drop associated with a 3% desaturation and/or arousal is 2.7 events/h. There were more frequent respiratory effort-related arousals (RERAs) as defined by flattening of the inspiratory portion of the nasal pressure signal immediately preceding arousals without meeting the definition of a hypopnea. Incorporating the apneas, hypopneas, and RERAs together, she experienced 17.8 events/h. Event-associated oxygen desaturations were mild and the oxygen saturation nadir was 92%. There was no significant positional component that was evident. The AHI was slightly higher in rapid eye movement (REM) sleep (6.4/h). Cardiac rhythm analysis was normal.

We explained to the patient that the PSG suggests that her sleep maintenance insomnia and daytime fatigue could be due to recurrent arousals that result from increased upper airway resistance during sleep. Treatment options were discussed, including a trial of continuous positive airway pressure (CPAP), a mandibular advancement device (MAD), and procedures on the upper airway. After trying on a CPAP mask in the office the patient stated that she did not think she would be able to sleep with it. A sample MAD was shown, which appeared to be more tolerable to the patient. She was referred to a sleep dentist, who provided the patient with a custom-fit MAD. After 6 weeks of use with gradual mandibular advancement to

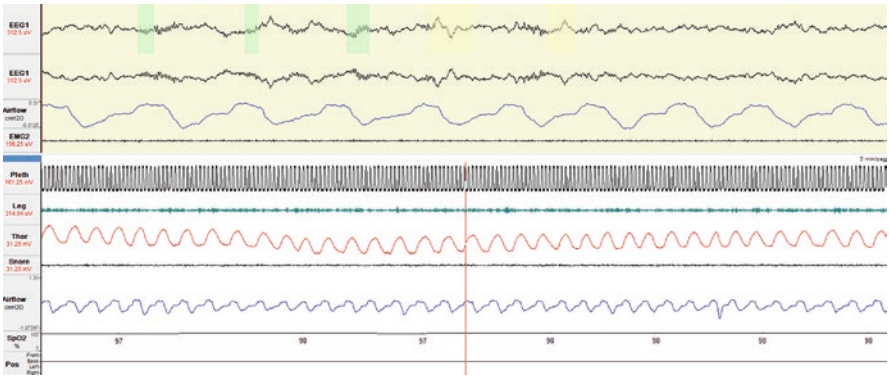


Fig. 9.2 Representative epoch from the follow up out-of-center sleep test with a mandibular advancement device demonstrates resolution of the inspiratory flow limitation on the nasal cannula/pressure transducer (blue)

10 mm, the patient reported improvement in her fatigue and sleep maintenance insomnia and her husband reported resolution of her snoring.

An out-of-center sleep test (OCST) with flow monitoring and limited electroencephalogram (EEG) montage while using the MAD revealed improved flow tracings with only rare flow limited breathing and RERAs occurring during REM sleep (Fig. 9.2). The overall event index combining apneas, hypopneas, and RERAs was reduced to 6 events/h. She elected to continue to use the MAD. She was seen in follow-up 6 months later and reported significant improvements in her sleep complaints. She does not require the use of regular hypnotics.

Discussion

Introduction

The term upper airway resistance syndrome (UARS) epitomizes the difficulty surrounding the ever-changing measurement techniques, shifting diagnostic criteria and lack of standardization in nomenclature that plagues the entirety of sleep medicine. To fully understand UARS as a diagnostic entity, one needs to appreciate the historical context surrounding its introduction.

UARS was first defined in adults in 1993 by Guilleminault et al. to describe a specific subset of patients previously diagnosed with idiopathic hypersomnia [1]. These patients had hypersomnia with frequent (>10/h) EEG arousals but did not meet criteria for obstructive sleep apnea (OSA). At the time, oronasal airflow was measured using thermal devices that detect changes between inspiratory and expiratory airflow temperature. This is effective in detecting apneas but does not vary proportionally to the magnitude of airflow and, therefore, poorly identifies

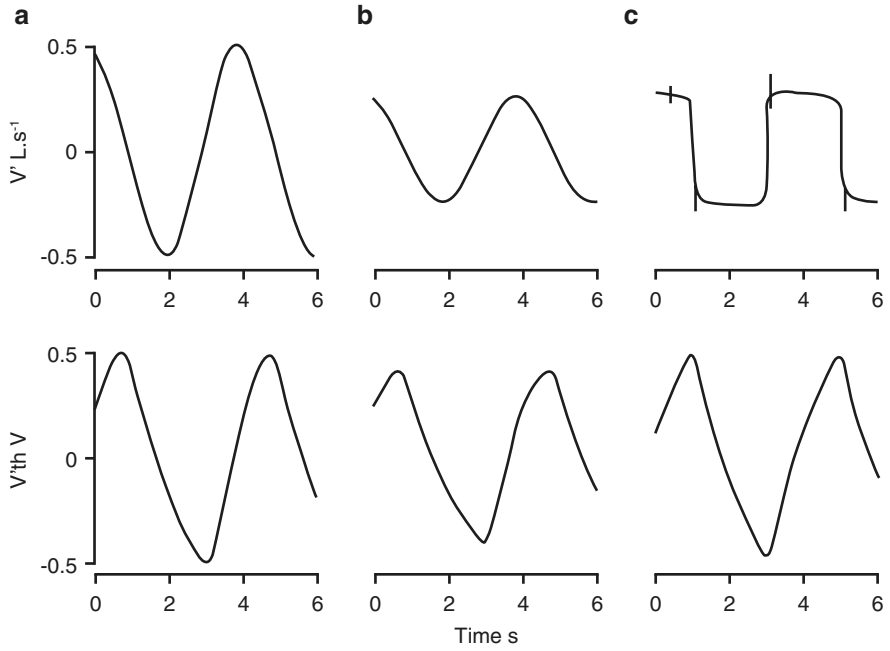


Fig. 9.3 Thermistors and airflow. Actual flow measured by the pneumotachography (*V'*) (top) and thermistor signal (*V'th*) recorded simultaneously. The thermistor signal (*V'th*) does not vary significantly in comparison to (**a**) despite large changes in amplitude (**b**) and morphology (**c**) of flow. (From Farré et al. [2])

hypopneas (Fig. 9.3) [2]. Guilleminault et al. used a pneumotachograph to quantify subtle changes in airflow and an esophageal probe to estimate changes in pleural pressure, which measures the respiratory effort that appears to be the primary stimulus in inducing arousals in a given respiratory event [3]. By using these two devices, the authors could identify increasing effort and calculate an increased resistance despite minimal changes in flow that preceded many of the patients' EEG arousals. These events did not meet apnea or hypopnea criteria, and thus the patients could not be diagnosed with OSA, despite the apparent shared pathophysiology. Thus, Guilleminault et al. identified a symptomatic population with abnormal breathing during sleep that had been previously ignored due to the constraints of the OSA criteria and the belief that sleep disordered breathing was synonymous with apneas and hypopneas.

The use of pneumotachographs and esophageal probes has proved impractical in routine PSG testing. However, the introduction of NC/PT as a semi-quantitative assessment of airflow has since obviated their need [4]. It was also demonstrated that the shape of the flow curve itself over the respiratory cycle on the NC/PT could reliably identify a pattern of inspiratory flow associated with passive airway collapse and associated with increased respiratory effort. When continuous over many breaths, this state has been labeled "inspiratory flow limitation (IFL)." Flattening of

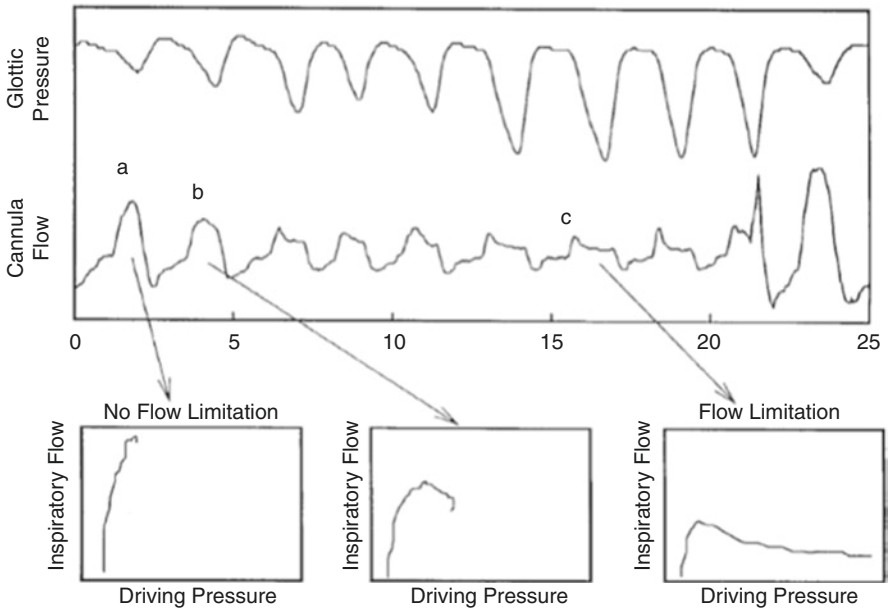


Fig. 9.4 Pressure/flow relationships during breathing. The x-axis is time. Breaths with normal (**a**), intermediate (**b**), and flattened (**c**) flow are labeled. Note the flattened flow-time contour shows nonlinear flow/pressure relationship characteristic of inspiratory flow limitation. (From Hosselet et al. [5])

the inspiratory airflow waveform contour on the NC/PT reliably identifies IFL when compared to the gold standard [5]. In addition, an increase in the inspiratory time to total respiratory cycle also aids in the non-invasive identification of IFL [6]. IFL correlates well with elevated effort as measured by esophageal balloon and can be used to non-invasively identify RERAs (Fig. 9.4) [7]. Snoring, the audible fluttering of the pharynx during inspiration, often, but not always, accompanies IFL. The non-invasive recognition of IFL thus identifies those patients who may have arousals due to increases in respiratory effort but do not meet the criteria for having frequent hypopneas or apneas.

The increased upper airway resistance events identified by Guilleminault et al. eventually became known as RERAs. UARS was a term given to the clinical entity of symptomatic patients with frequent RERAs but AHIs <5 events/h. Since most desaturating events would have met the criteria for apnea or hypopnea, patients with UARS generally have oxygen nadirs that remain ≥90% over the course of the night. The specific criteria used by authors to define UARS has varied significantly across studies but most required the presence of symptoms in the setting of a PSG that is negative for OSA (as defined by an AHI < 5 events/h) but demonstrates frequent arousals (thus fragmented sleep) as a result of elevated upper airway resistance [8]. Accompanying oxyhemoglobin desaturations are mild. In an updated review in 2012, Guilleminault et al. defines the UARS as symptoms with an AHI < 5 events/h

on PSG, oxygen saturation nadir >92%, and the presence of RERAs and other non-apnea/hypopnea respiratory events [9].

The introduction of this clinical syndrome created controversy, mainly because many believed that RERAs and hypopneas were similar entities and that OSA and UARS ultimately describe sleep fragmentation and hypersomnolence due to intermittent increases in upper airway resistance. It was argued that the discovery of UARS reflected advances in measurement techniques rather than the description of a previously unknown clinical entity. The most recent International Classification of Sleep Disorders (ICSD-3) agrees with this concept, and the term UARS is subsumed under the diagnosis of OSA [10]. OSA threshold criteria are based on the combined frequency of all the increased resistive events: apneas, hypopneas and RERAs, defined according to the American Academy for Sleep Medicine Manual for the Scoring of Sleep and Associated Events. While there are still theoretically cases of respiratory events that do not strictly meet RERA criteria but are still associated with increased respiratory effort due to increased upper airway resistance (e.g., a resistive event that lasts less than 10 s or results in a shift in EEG frequency that does not meet standard arousal criteria), in practice, most patients previously diagnosed with UARS can be diagnosed with OSA using the ICSD-3 criteria. Our patient, when incorporating all the resistive events including RERAs into the AHI, would meet criteria for OSA using this definition. The term UARS still exists in the literature and is used in clinical practice, however; thus familiarity with it is necessary for practitioners of sleep medicine. Our practice uses UARS to describe symptomatic patients who experience frequent arousals during sleep with long periods of IFL and few desaturating events. The total apneas and hypopneas on a PSG are generally less than 5 events/h, especially when using the alternate criteria requiring a 4% desaturation, but there are frequent RERAs.

Epidemiology

There are few large-scale epidemiologic studies examining the prevalence of UARS in the general population. Habitual snoring is seen in up to 50% of individuals. Snoring usually accompanies IFL, but snoring is not synonymous with UARS, as it occurs in people both with OSA and those without symptoms – two populations who by definition do not have UARS. The use of snoring to describe UARS epidemiology, as is sometimes done in the literature, is therefore inaccurate [11]. In one study of mostly non-obese patients referred to a sleep center predominantly for loud and disruptive snoring, the authors discovered a 41% prevalence of UARS; the remaining patients mostly had OSA [12]. A retrospective review of military recruits with hypersomnolence who underwent PSG found the prevalence of UARS to be 8.4% [13]. Both these studies, however, do not address the prevalence of UARS in the general population. Palombini et al. evaluated the distribution of IFL during sleep from an asymptomatic population in Brazil [14]. From these normative data it was found that only 5% of asymptomatic individuals have >30% of total

sleep time with IFL, suggesting a cutoff value >30% of total sleep time in IFL may be used to help define the presence of SDB and that <30% time spent with IFL may be normal.

Clinical Presentation

The symptoms of UARS overlap with those of OSA. Snoring is common, but not necessary as snoring is notoriously subjective, with poor inter-rater agreement between individual and the bed partner and has only a weak correlation with objective PSG data [11]. In addition, despite IFL being a characteristic, if not defining, component of UARS, it is not accompanied by objective snoring in 9.1% of patients, so called "silent UARS" [13]. Reports of witnessed apneic events do not preclude the diagnosis of UARS; one third of patients may have witnessed apneas despite not meeting the AHI threshold criteria for OSA [15]. While diurnal sleepiness remains a main diagnostic criteria, up to 20% of patient with UARS may actually report chronic insomnia. As in the patient in the case presentation, this often leads to delays in diagnosis and inappropriate treatment with hypnotics. Fatigue, as opposed to sleepiness, is also commonly reported [9]. Functional somatic complaints, such as irritable bowel syndrome, headaches, anxiety, depression, and fibromyalgia, are also more common in the UARS population, as is the finding of alpha-delta sleep [15, 16]. The reasons for these associations are speculative but have caused some to propose that the UARS population is a subset of a group that has "inappropriate" responses to autonomic stimuli (see ref. [15]).

In comparison to their OSA counterparts, most studies have found that patients with UARS are younger (mean age is around 40 years), thinner (mean body mass index <25 kg/m^2), and more frequently female (about 50%) [3, 16, 17]. Additionally, as in our patient, mild craniofacial differences may be noted, including a narrow, elongated face, vaulted palate, reduced mouth opening, and dental overjet [12, 18]. These associations may represent the phenotype of a separate entity, but it has been pointed out that they also are the characteristics of subjects who tend to have the mildest upper airway obstruction. These findings are not specific and PSG testing is required to confirm the diagnosis.

While a great deal of research has attempted to define the cardiovascular consequences of OSA, there has been scant investigation into this realm for patients with UARS. Suboptimal CPAP to induce prolonged IFL in subjects with OSA did not lead to changes in systemic blood pressure swings during sleep in one study [19]. Another study showed repetitive increases in blood pressure did result from increased airway resistance during sleep in the absence of classic apneas and hypopneas and that some patients with borderline hypertension can improve their blood pressure with treatment of UARS [20]. Further study is required in this area.

Polysomnographic Findings

The UARS patient will not have many obstructive apneas and hypopneas (by most definitions, it will be <5/h) but will display frequent and often sustained periods of IFL (see Fig. 9.1) terminating in arousal (RERAs). Patients may show other evidence of elevated upper airway resistance such as snoring, choking, gasping, or frequent unexplained arousals. The frequency of these RERAs is usually between 5 and 20/h. As opposed to OSA, UARS has not been sub-classified into severity levels on the basis of event frequency, in part because the events can be very prolonged and thus have a low total count. Most sleep study reports are descriptive rather than quantitative in describing IFL, and it is not routinely scored or quantified. In addition, the amount that defines abnormal is not definitively known, although the aforementioned study by Palombini et al. estimates that the 95% confidence limit of the percent of time spent in IFL in normal subjects is 30% of sleep time [14].

The original conceptual pathophysiologic model of how UARS leads to fatigue and hypersomnolence was that respiratory arousals lead to sleep fragmentation and frequent stage shifts as well as decreased slow wave sleep, akin to what occurs in OSA [17]. Further study using power spectral EEG analysis has identified differences in sleep quality that extend beyond simple intervening arousals. Alpha EEG frequency time during non-rapid eye movement sleep is high in UARS patients and may reflect a state of arousal, nonrestorative sleep. This may explain some of the particular sleep complaints unique to UARS patients such as complaints of nonrestorative sleep or insomnia. Cyclic alternating pattern, a manifestation of nonrestorative unstable sleep, is also more frequent in UARS patients than controls [15, 16].

Pathophysiology

Most sleep researchers believe that the IFL observed in patients with UARS results from narrowing of the pharyngeal airway due to relaxation of the pharyngeal dilator muscles, essentially identical to the pathophysiology of OSA. Pharyngeal collapse depends on the balance between collapsible and protective factors. The pharyngeal "critical pressure" (Pcrit), the pressure below which the pharynx will collapse, is very negative in normal subjects and progressively less negative as the severity of OSA increases, reaching values above zero in severe OSA. Pcrit in patients with UARS is intermediate between controls and those with OSA [21]. UARS patients are thus able to maintain flow at a higher level of upper airway resistance in any sleep stage compared to OSA patients. They may also have an altered arousal response to the elevated resistance. Thus, for the same level of respiratory effort, UARS patients can maintain a patent airway (albeit with flow limitation) instead of progressing to apneas or frank hypopneas [16]. This may be in part due to differences in local pharyngeal reflexes. Patients with OSA may have

a local demyelinating neuropathy at the pharyngeal region as a result of repetitive vibration trauma from chronic snoring, with resultant altered oropharyngeal sensory thresholds and abnormal evoked responses to respiratory stimuli, findings that are absent in UARS patients [9]. This suggests that OSA patients have neurogenic lesions that interfere with the normal control of upper airway patency, while UARS patients activate airway-protective reflexes with the consequence of high levels of dilating muscle activity to counteract the increased upper airway resistance [16]. It is possible that the sustained challenge of increased resistance on the upper airway, along with intervening arousals when the esophageal pressure nadir threshold is reached, activates a stress response for many hours per night, leading to symptoms that accompany the chronic stress response, such as insomnia, gastrointestinal irritability, and anxiety. While many consider UARS to be the mildest form of OSA, some studies have actually demonstrated worse daytime functional impairment in patients with UARS in comparison to mild OSA, including worse perceived sleep quality, more fatigue and worse early morning sustained attention [22].

Treatment

A long-term outcome study (4.5 years) in patients with UARS that were not treated found an up to 20-fold increase of sleep related complaints including fatigue, insomnia, and depressive mood, despite no significant changes in the AHI. These patients were frequently prescribed hypnotics, antidepressants, and stimulants for these symptoms [23]. These findings imply that long-term treatment is warranted. In the original paper by Guilleminault et al., nasal CPAP reduced transient arousals, abnormal upper airway resistance, and eliminated daytime sleepiness (as documented by multiple sleep latency testing) in the subgroup of patients they diagnosed as having UARS. Interestingly, they specifically recommended against CPAP as a long-term treatment of this syndrome [1]. Only a few trials have investigated CPAP specifically in patients with UARS. Improvements in both objective sleep parameters and subjective symptoms have been found in some but not all studies [3, 8]. If used, CPAP should be titrated to eliminate IFL on the CPAP tracing during the CPAP titration study. Mean therapeutic levels of CPAP tend to be low. Our experience is that CPAP delivered via a nasal rather than an oronasal mask is more effective to eliminate IFL during sleep; thus we avoid oronasal masks in this population. Auto-titrating CPAP algorithms often are designed to eliminate IFL; thus, they should be an acceptable mode of treatment though this has not been specifically studied. While physiologically effective, long-term compliance with CPAP remains a challenge, a phenomenon shared with the OSA population [8]. Obtaining insurance approval to cover the costs of the CPAP supplies can also be difficult and hinder treatment [23]. One approach to CPAP use in UARS is the “therapeutic

trial," focusing on demonstration of relief of symptoms as a goal, rather than immediately prescribing long-term use. This may help cement the diagnosis, after which more acceptable but less consistently effective treatment may be tried.

MADs appear to be an effective alternative to CPAP in UARS. One randomized, placebo-controlled study found improvements in many sleep parameters and quality of life scores after 1.5 years in patients with UARS [24]. Other small studies and case series echo these findings [8]. Side effects are minor, especially in the hands of a dentist experienced in sleep medicine. We often find that patients with UARS are more inclined to pursue treatment with MADs than CPAP when both are shown in the clinic, especially when insomnia is present.

Surgical options are appealing given the craniofacial abnormalities that may be present in patients with UARS, but many of the traditional surgical procedures used for OSA may be considered too aggressive. Few randomized trials are available that specifically study patients with UARS. In patients who prefer surgery as treatment, it is logical that the procedures should address the anatomic region(s) causing upper airway obstruction. These include septoplasty, turbinate reduction, laser-assisted uvuloplasty, genioglossus bone advancement, and hyoid myotomy with suspension. Rapid maxillary distraction is effective in children but may not be practical in adults due to maxillary and mandibular ossification. The small studies that exist report improvement in symptoms, but conclusions are limited due to the lack of objective data, variable diagnostic criteria, and paucity of long-term outcomes [3, 9]. A specifically focused randomized prospective trial is needed, unless it is assumed that UARS is similar to "mild" OSA. Before referring patients to our surgical colleagues, we try to establish therapeutic response to more conservative treatments, such as CPAP or MAD, to decrease the chance of an ineffective surgery.

Weight loss reduces snoring and lowers pharyngeal Pcrit and is thus a logical first step in the management of overweight or obese patients with UARS, and one that is likely to have beneficial effects beyond just sleep disordered breathing [25]. Positional therapy can also be trialed in this population. Treatment of any nasal obstruction present is also recommended although it should be noted that despite improving nasal resistance, the effect on respiratory events is generally small if this is the only treatment pursued. In children, however, relief of elevated chronic upper airway obstruction by tonsil and adenoidal hypertrophy, with or without a syndrome not dissimilar to UARS, may be particularly important to prevent the development of the adenoid facies and craniofacial abnormalities, which in turn may predispose patients to UARS.

Treating sleep fragmentation in UARS with hypnotics without addressing the underlying etiology of increased upper airway resistance is misguided but unfortunately common. Symptoms are not effectively controlled long-term, although short-term hypnotic use as an adjuvant to definitive UARS therapy in patients with coexisting insomnia is reasonable [8].

Conclusion

The sleep community's understanding of sleep disordered breathing has evolved from recognizing clear obstructive apneas that were evident on thermistors and associated with severe oxygen desaturations to that of identifying the mildest IFL associated with subtle EEG arousals. Beyond its potential clinical implications, the UARS as a concept was important to help move the field of clinical sleep medicine to consider that sleep disordered breathing existed outside of the limits of the AHI. It is unclear if the incorporation of UARS into the OSA definition, despite possible differences in clinical presentation, polysomnographic findings and treatment options, will limit its future research and recognition.

Clinical Pearls

- The term UARS was introduced to capture a population of patients who clinically differed from their OSA counterparts but had been largely ignored due to limitations of diagnostic methods.
- Patients with UARS experience prolonged periods of inspiratory flow limitation, have frequent arousals due to increased upper airway resistance, and have attributable symptoms but do not have enough respiratory events that meet the definition of hypopneas or apneas to be diagnosed with OSA.
- The updated ICSD-3 has included these events, partially captured by the term RERAs, in their overall definition of OSA. With the most recent preferred definition of hypopnea (2018) from the AASM, most people who had previously been diagnosed with UARS will now meet the criteria for OSA.
- Patients with UARS are often described as more likely to be female, younger, leaner, more prone to functional somatic disorders and have more particular craniofacial findings than their OSA counterparts. They are more likely to complain of fatigue and insomnia as opposed to excessive sleepiness.
- Treatment for UARS is similar to that of OSA, focusing on decreasing the resistance of the upper airway during sleep. It includes CPAP, MADs, otolaryngology procedures, positional therapy, and weight loss.

References

1. Guilleminault C, Stoohs R, Clerk A, Cetel M, Maistros P. A cause of excessive daytime sleepiness: the upper airway resistance syndrome. Chest. 1993;104:781–7.
2. Farré R, Montserrat JM, Rotger M, Ballester E, Navajas D. Accuracy of thermistors and thermocouples as flow-measuring devices for detecting hypopneas. Eur Resp J. 1998;11:179–82.
3. Exar EN, Collop NA. The upper airway resistance syndrome. Chest. 1999;115:1127–39.

4. Montserrat JM, Farré R, Ballester E, Felez A, Pastó M, Navajas D. Evaluation of nasal prongs for estimating nasal flow. Am J Respir Crit Care Med. 1997;155:211–5.
5. Hosselet JJ, Norman RG, Ayappa I, Rapoport DM. Detection of flow limitation with a nasal cannula/pressure transducer system. Am J Respir Crit Care Med. 1998;157:1461–7.
6. Mooney AM, Abounasr KK, Rapoport DM, Ayappa I. Relative prolongation of inspiratory time predicts high versus low resistance categorization of hypopneas. J Clin Sleep Med. 2012;8:177–85.
7. Ayappa I, Norman RG, Krieger AC, Rosen A, O'Malley RL, Rapoport DM. Non-invasive detection of respiratory effort-related arousals (RERAs) by a nasal cannula/pressure transducer system. Sleep. 2000;23:763–71.
8. de Godoy LB, Palombini LO, Guilleminault C, Poyares D, Tufik S, Togeiro SM. Treatment of upper airway resistance syndrome in adults: where do we stand? Sleep Sci. 2015;8:42–8.
9. Guilleminault C, De Los Reyes V. Upper-airway resistance syndrome. Handb Clin Neurol. 2011;98:401–9.
10. American Academy of Sleep Medicine. International classification of sleep disorders. 3rd ed. Darien: American Academy of Sleep Medicine; 2014. p. 53–62.
11. Stoohs R, Gold AR. Snoring and pathologic upper airway resistance syndromes. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. 6th ed. Philadelphia: Elsevier; 2017. p. 1088–101.
12. Guilleminault C, Black JE, Palombini L, Ohayon M. A clinical investigation of obstructive sleep apnea syndrome (OSAS) and upper airway resistance syndrome (UARS) patients. Sleep Med. 2000;1:51–6.
13. Kristo DA, Lettieri CJ, Andrada T, Taylor Y, Eliasson A. Silent upper airway resistance syndrome; prevalence in a mixed military population. Chest. 2005;127:1654–7.
14. Palombini LO, Tufik S, Rapoport DM, Ayappa IA, Guilleminault C, de Godoy LB, Castro LS, Bittencourt L. Inspiratory flow limitation in a normal population of adults in São Paulo, Brazil. Sleep. 2013;36:1663–8.
15. Gold AR, Dipalo F, Gold MS, O'Hearn D. The symptoms and signs of upper airway resistance syndrome; a link to the functional somatic syndromes. Chest. 2003;123:87–95.
16. Pepin JL, Guillot M, Tamisier R, Levy P. The upper airway resistance syndrome. Respiration. 2012;83:559–66.
17. Stoohs RA, Knaack L, Blum HC, Janicki J, Hohenhorst W. Differences in clinical features of upper airway resistance syndrome, primary snoring, and obstructive sleep apnea/hypopnea syndrome. Sleep Med. 2008;9:121–8.
18. de Godoy LB, Palombini LO, Haddad FL, Rapoport DM, Vidigal TA, Klichouvicz PC, Tufik S, Togeiro SM. New insights on the pathophysiology of inspiratory flow limitation during sleep. Lung. 2015;193:387–92.
19. Calero G, Farre R, Ballester E, Hernandez L, Daniel N, Canal JM. Physiological consequences of prolonged periods of flow limitation in patients with sleep apnea hypopnea syndrome. Respir Med. 2006;100:813–7.
20. Guilleminault C, Stoohs R, Shiomi T, Kushida C, Schnittger I. Upper airway resistance syndrome, nocturnal blood pressure monitoring, and borderline hypertension. Chest. 1996;109:901–8.
21. Gold AR, Marcus CL, Dipalo F, Gold MS. Upper airway collapsibility during sleep in upper airway resistance syndrome. Chest. 2002;121:1531–40.
22. de Godoy LB, Luz GP, Palombini LO, Silva LO, Hoshino W, Guimaraes TM, Tufik S, Bittencourt L, Togeiro SM. Upper airway resistance syndrome patients have worse sleep quality compared to mild obstructive sleep apnea. PLoS One. 2016;11:1–12.
23. Guilleminault C, Kirisogly C, Poyares D, Palombini L, Leger D, Farid-Moayer M, Ohayon MM. Upper airway resistance syndrome: a long-term outcome study. J Psychiatry Res. 2006;40:273–9.
24. Godoy LB, Palombini L, Poyares D, et al. Long-term oral appliance therapy improves daytime function and mood in upper airway resistance syndrome patients. Sleep. 2017;4(12):zsx175.
25. Montserrat JM, Badia JR. Upper airway resistance syndrome. Sleep Med Rev. 1999;3:5–21.

Chapter 10
Sleep Apnea in Pregnancy

Jisoo Lee and Katherine M. Sharkey

Case

Ms. E is a 38-year-old woman with a past medical history of hypertension, depression, obesity, headaches, and anemia who reported insomnia during a routine visit with her obstetrician at 18 and 5/7 weeks' gestation and was referred for further sleep evaluation. Ms. E stated that she was having increasing difficulty staying asleep, and was experiencing light, fragmented sleep for the last 2 months. She usually got up to urinate twice per night and was able to fall back to sleep within a few minutes after each awakening, but sleep quality was poor. Although she had always had some snoring, this had worsened in the last several weeks. Ms. E also noted that her husband told her that he had noticed pauses in her breathing during sleep. Associated symptoms included morning tiredness, nasal congestion, postnasal drip, night sweats, nocturia, gastroesophageal reflux, and worsening of her headaches.

She denied parasomnia behaviors, restless legs symptoms, leg kicking, sleep paralysis, and sleepiness while driving. Her Epworth Sleepiness Scale score was 14/24, and she noted a particularly high propensity for dozing while watching TV and while purposely lying down to rest in the afternoon. She reported napping 1–2 times/week for up to 1 h and although overall she felt that naps were refreshing, she also stated that she sometimes had a headache or felt groggy after a nap.

Medications included acetaminophen, ferrous sulfate, meclizine, and prenatal vitamins. The patient was a nonsmoker and drank 1–2 cups of caffeinated coffee each morning. She did not smoke or use recreational drugs.

J. Lee
Rhode Island Hospital, Pulmonary, Critical Care Medicine and Sleep, Providence, RI, USA

K. M. Sharkey (✉)
The Warren Alpert Medical School of Brown University, Providence, RI, USA
e-mail: Katherine_sharkey@brown.edu

C. Won (ed.), *Complex Sleep Breathing Disorders*,
https://doi.org/10.1007/978-3-030-57942-5_10

On physical exam, the patient was 62″ tall and weighed 218 lbs, yielding a body mass index of 40.1 kg/m^2. Blood pressure was 124/68 mmHg and pulse was 95 bpm. Oxygen saturation was 98.1% on room air. Head and neck exam showed bilaterally patent nares, a Mallampati class 4 airway, and a narrow posterior oropharynx with a deep-set uvula and soft palate. Neck circumference was 14″, and no masses, lymphadenopathy, or thyromegaly were present. Cardiac and pulmonary exams were normal. Distal pulses were intact, and the patient had trace pedal edema bilaterally.

An in-laboratory sleep study was recommended to the patient, but she was worried that she would not be able to sleep in the laboratory and had concerns about finding child care for her son given her husband's work schedule as a firefighter. Thus, the patient was scheduled for a home sleep study (HST), which was performed at 22 weeks' gestation. She wore the recorder for 471 min, during which she had 4 obstructive apneas and 142 hypopneas yielding a 4% oxygen desaturation. Thus, her overall respiratory event index (REI) was 18.6 events/h of recording. Oxygen saturation minimum was 76% and she spent 8.6% of the recording with an oxygen saturation lower than 90%. Sleep apnea was significant in all body positions (supine REI was 18.9 events/h; non-supine REI was 16.5 events/h). Moderate-to-loud snoring was observed. Average heart rate was 88 bpm.

After the diagnosis of OSA was established, the patient was started on auto-titrating CPAP with a low pressure of 6 cmH_2O and a high pressure of 16 cmH_2O. Median pressure was 9.7 cmH_2O. Ms. E had suboptimal compliance with CPAP therapy, using only 46% of nights and averaging daily use of just 3 h and 20 min. The patient reported that she frequently fell asleep on the couch watching TV and then when she woke up and went to bed, she was too tired to apply her CPAP mask. On nights when she did remember to use her CPAP, she would fall asleep with the mask on, but when she took it off to use the bathroom for the first time during the night, she rarely reapplied the CPAP when she got back in bed.

The patient delivered a healthy male infant at 39 3/7 weeks' gestation. He weighed 8 lbs., 4 oz., and Apgar scores were 9 at 1-min and 10 at 5-min. Ms. E exclusively breastfed her son for the first 7 weeks postpartum and then supplemented with formula thereafter. Her baby was healthy and reportedly met early developmental milestones appropriately.

The patient was seen at 3-months postpartum. She reported that she never used her CPAP machine after delivery. Her son was waking 1–3 times per night and was awake about 30–40 min each time. She estimated that she obtained about 6–7 h of sleep each night, typically between the hours of 11 pm and 8:30 am. She lost 25 lbs. (new weight = 193 lbs.) and her body mass index was reduced to 35.3 kg/m^2. She still had occasional snoring, but overall she felt she was sleeping well, aside from the night awakenings to provide infant care.

A repeat HST was performed at 3-months postpartum. Ms. E wore the recorder for 293 min and had zero apneas and 15 4%-hypopneas for an REI of 3.1 events/h. There was no positional component. Oxygen saturation minimum was 85%, but she spent <1% of the recording with an oxygen saturation lower than 90%. Intermittent, moderate snoring was heard.

With resolution of her OSA demonstrated on repeat HST, CPAP was discontinued. Ms. E was counseled to be aware of signs or symptoms that her sleep apnea had returned with weight gain, subsequent pregnancies, and/or aging.

The case of Ms. E highlights many features and challenges of diagnosing and managing sleep apnea during the perinatal period, as discussed below.

Discussion

Normal Respiratory Physiology Changes During Pregnancy

Pregnancy causes significant changes in respiratory physiology during sleep across multiple systems, including anatomical alterations in the airway, hormonal influences, and mechanical changes. Upper respiratory tract changes begin in the first trimester and persist throughout pregnancy. These changes include mucosal edema, hyperemia, capillary congestion, and upper airway fragility [1]. Nasal airway edema decreases nasal patency, reducing pharyngeal size and increasing Mallampati score [2], thereby increasing risk of airflow limitations.

Hormonal fluctuations throughout gestation also impact respiratory physiology. Estrogen increases during pregnancy and can affect nasal mucosa and contribute to rhinitis symptoms, whereas higher progesterone levels stimulate ventilatory drive to increase minute ventilation up to 50% by increasing the tidal volume and respiratory rate [1]. Oxytocin that peaks at night may cause sleep fragmentation in late pregnancy [3].

Changes also occur in the thoracic anatomy as well as in lung volumes and function. The subcostal angle increases and the diaphragm is elevated in pregnancy [1]. Functional residual capacity decreases due to elevated diaphragm and decreased lung compliance [1]. Oxygen consumption is increased in pregnancy and arterial oxygen content is lower in pregnancy due to physiologic anemia [1]. However, oxygen delivery is maintained by increased cardiac output by 50%.

Sleep-Disordered Breathing in Pregnancy

The cascade of physiologic, anatomic, and endocrine changes associated with pregnancy described above lead to obstructive respiratory events and predispose pregnant women to the spectrum of sleep-disordered breathing (SDB). SDB is a group of disorders characterized by abnormal respiratory patterns due to impaired airflow or abnormal gas exchange due to upper airway narrowing or inefficiency of the ventilatory systems [4, 5]. SDB encompasses a continuum of disorders including snoring, upper airway resistance syndrome, sleep apnea, and sleep-related hypoventilation disorders.

Obstructive sleep apnea is a common type of SDB and is defined by multiple breathing cessations (apneas) or partial airway obstructions (hypopneas) that occur throughout the night and result in arousals and awakenings from sleep and intermittent hypoxia. When apneas and hypopneas occur chronically, consequences include hypercarbia, insulin resistance, sympathetic activation, endothelial cell dysfunction, daytime sleepiness, and increased risk of mood dysregulation and cognitive impairment.

The prevalence of SDB in pregnancy is not well known. It is thought that SDB is frequently underdiagnosed in this population as symptoms vary widely and can overlap with other phenomena that are common during pregnancy, e.g., nocturia, fatigue. Furthermore, polysomnography is not commonly ordered for pregnant women. With increasing prevalence of obesity and increasing maternal age, it is postulated that the prevalence of SDB is increasing. In a cross-sectional survey of 1000 immediately postpartum women, 35.1% of new mothers reported snoring during the last 3 months of pregnancy, and 37% of subjects reported having at least one SDB symptom derived from the Multivariable Apnea Prediction Index (MAPI [6]) (loud snoring, snorting/gasping, breathing stoppage, choking, or struggling to breathe) [7].

The prevalence of OSA among reproductive age women is estimated between 0.7 and 7%, and the prevalence among pregnant women is estimated between 11% and 20% [8]. An analysis of data on nearly 56 million inpatient hospital stays of US women who were pregnant or gave birth between 1998 and 2009 from the Nationwide Inpatient Sample (NIS) database used International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes to estimate OSA prevalence [8]. OSA was diagnosed in 3 out of 10,000 women (95% CI, 2.8–3.2). The prevalence of perinatal OSA diagnosis climbed over the study period, from 0.7 per 10,000 population in 1998 to 7.3 per 10,000 population in 2009, which may reflect the increase in the prevalence of obesity during the same time period, as well as increased recognition or coding of the diagnosis of sleep apnea in this population.

The Nulliparous Pregnancy Outcomes Study Monitoring Mothers-to-be (NuMoM2b) prospective cohort study also provides important data about prevalence of SDB during pregnancy [9]. In NuMom2b, HSTs were performed in first trimester (6–15 weeks' gestation, $n = 3132$) and repeated in a subset of women during second trimester (22–31 weeks' gestation, $n = 2474$). Using an apnea-hypopnea index (AHI) $\geq$ 5/h to define sleep-disordered breathing, the prevalence of sleep-disordered breathing was 3.6% and 8.3%, in first and second trimester, respectively.

There are several risk factors for OSA in pregnant women. As mentioned, during pregnancy, there is weight gain, increased airway edema, nasal congestion (i.e., rhinitis of pregnancy), as well as reduced lung functional reserve capacity. Moreover, in early pregnancy, there is more time spent sleeping in supine position. Older age and obesity are both independent risk factors for OSA. Chronic hypertension, gestational diabetes, history of preeclampsia, and/or a twin gestation are also known to increase the risk [4].

There are protective factors for SDB in pregnancy which include high progesterone level, improved oxygen delivery, and less time spent sleeping in the supine position particularly in later pregnancy [10]. Progesterone stimulates ventilatory drive by acting at the level of the central chemoreceptors on the ventrolateral surface of the medulla, and increases minute ventilation, decreases end-tidal carbon

dioxide, and lowers upper airway resistance [11]. Progesterone also increases electromyographic activity of the upper airway dilator muscle, leading to less airway collapsibility and thus protecting from obstruction [12].

Diagnosis of SDB in Pregnancy

The gold standard diagnostic test for the diagnosis of OSA in pregnant women is in-laboratory polysomnography [13]. Because most HSTs measure only respiratory parameters and not whether the patient is asleep, HSTs are less reliable for the pregnant population and can underestimate sleep apnea as sleep fragmentation and disturbances are common among pregnant women. There is also concern with the accuracy of HSTs in advanced pregnancy when the gravid abdomen may displace thoracoabdominal belts. However, many of the large studies that guide OSA prevalence estimates and outcomes in pregnancy have been based on HSTs. Similarly, sleep apnea screening questionnaires that are validated in non-pregnant populations are not reliable in pregnancy [14]. There is little evidence to guide the timing of sleep testing during pregnancy, or the need for repeat testing in pregnant women at risk for SDB. As in our patient, the severity of SDB may change after delivery, and repeat testing is likely warranted to re-evaluate the ongoing need for therapy. However, at what point after delivery sleep testing should occur is again based on limited evidence.

Sleep Apnea in Pregnancy Affects the Health of Mother and Infant

SDB in pregnancy is associated with adverse maternal outcomes. Louis and colleagues' examination of >55 million pregnancy-associated hospitalizations in the Nationwide Inpatient Sample database from 1998 to 2009 demonstrated that women whose records included a diagnosis of sleep apnea were 2.5 times more likely to be diagnosed with preeclampsia (OR, 2.5; 95% CI, 2.2–2.9) [8]. Importantly, this study also showed associations between a diagnosis of OSA and critical medical outcomes including eclampsia (OR, 5.4; 95% CI, 3.3–8.9), cardiomyopathy (OR, 9.0; 95% CI, 7.5–10.9), pulmonary embolism (OR, 4.5; 95% CI, 2.3–8.9), and in-hospital mortality (95% CI, 2.4–11.5). Comorbid obesity further increased the risk of these untoward outcomes associated with OSA.

Similarly, in a national cohort study by Bourjeily et al., pregnant women with OSA had a significantly higher risk of pregnancy-specific complications compared to pregnant women without OSA [15]. The complications included gestational hypertensive conditions, gestational diabetes (GDM), cardiomyopathy, pulmonary edema, congestive heart failure, and hysterectomy. OSA was also associated with a longer hospital stay and significantly increased odds for intensive care unit admission [15].

The NuMoM2b study also showed associations between sleep-disordered breathing and preeclampsia, hypertensive disorders of pregnancy, and GDM [9]. This prospective cohort study showed that SDB was associated with preeclampsia in early (OR 1.94, 95% CI 1.07–3.51) and mid-pregnancy (OR 1.95 with 95% CI 1.18–3.23). For SDB and hypertensive disorders of pregnancy, the OR was 1.46 (95% CI 0.91–2.32) and 1.73 (95% CI 1.19–2.52) for early and mid-pregnancy, respectively. SDB was also associated with gestational diabetes with odds ratios of 3.47 (95% CI 1.95–6.19) in early pregnancy and 2.79 (95% CI 1.63–4.77) in mid-pregnancy [9]. Increasing exposure-response relationships were observed between AHI and both hypertensive disorders and gestational diabetes [9]. Increased inflammatory response is one possible mechanism linking sleep apnea and gestational diabetes to untoward health outcomes [16].

In another study of 175 pregnant women with obesity, OSA was associated with more frequent Caesarean delivery (65.4% compared with 32.8%), preeclampsia (42.3% compared with 16.9%), and neonatal intensive care unit admission (46.1% compared with 17.8%) [17].

Although snoring is considered a milder form of SDB, patients' self-reports of snoring are also associated with worse pregnancy outcomes. For example, unplanned Caesarean deliveries were more likely to occur in pregnant women who reported snoring compared to those that reported no snoring, even after adjusting for potential confounders [7]. A distinction has been made between habitual snoring that existed pre-pregnancy and new-onset snoring. Among 1712 pregnant women surveyed by O'Brien et al. [18], 34.1% reported snoring during third-trimester, including 9% who reported that snoring existed prior to pregnancy and 25% that reported new-onset snoring. Pregnancy-onset, but not chronic, snoring was independently associated with gestational hypertension (OR 2.36, 95%CI 1.48–3.77) and preeclampsia (OR 1.59, 95%CI 1.06–2.37) after controlling for potential confounding variables such as maternal age, pre-pregnancy BMI, gravidity, smoking, and previous or family history of gestational hypertension or preeclampsia. Proposed mechanisms for the observed link between new-onset snoring and pregnancy-related hypertensive disorders are an area of active investigation and include inflammation, endothelial cell dysfunction, increased erythropoiesis, and oxidative stress. The clinical implication of these findings is that inquiring about snoring and the timing of its onset during pregnancy may help identify women at risk for gestational hypertension and preeclampsia.

SDB in pregnancy also carries a potential risk for adverse neonatal outcomes. In a Swedish study with 502 pregnant women, snoring was a significant predictor of growth retardation (OR 3.45; $p < 0.01$), and an Apgar score less than or equal to 7 at 1-min and 5-min were more common in infants born to habitual snorers [19]. In another study by Chen et al., pregnant women with OSA had higher adjusted odds ratios for low birthweight (1.76, 95% CI 1.28–2.40), preterm births (2.31, 95% CI 1.77–3.01), and small for gestational age (SGA) infants (1.34, 95% CI 1.09–1.66) [20]. Pregnant women with OSA had unadjusted odds ratio of 10.11 (95% CI 3.45–29.67) for a low 5-min Apgar score [20]. Maternal SDB may affect neurocognitive or social development of the infant, but more investigations are needed to draw conclusions [21].

Treating Sleep Disordered Breathing in Pregnancy

These detrimental findings with SDB in pregnancy are relatively recent, and therefore, management of SDB in expectant mothers is guided by clinical experience, standard-of-care, and data in the non-pregnant population, rather than well-defined clinical trials in perinatal women. Based on a robust literature showing that CPAP therapy improves symptoms and medical comorbidities associated with OSA among non-pregnant adults, CPAP is also the gold standard therapy for treating SDB in pregnant women. The goal of CPAP is to eliminate abnormal respiratory events, i.e., reduce AHI. Clinicians treating pregnant women often prescribe auto-titrating CPAP, which has several advantages including (a) faster initiation of therapy from time of diagnosis because patients do not have to wait for laboratory CPAP titration; (b) increased access to treatment in regions where in-laboratory polysomnography is less available; and (c) the ability of auto-titrating CPAP to accommodate weight gain and upper airway changes that occur as pregnancy progresses. The ability of clinicians to access patients' CPAP use and estimated efficacy data from downloads of modern CPAP devices also allows for hands-on management of OSA during the dynamic time of pregnancy.

CPAP therapy is the most common therapy for OSA in pregnancy, but the degree to which pregnant women with SDB benefit from CPAP therapy and whether CPAP treatment mitigates risks associated with SDB during pregnancy is not well described. Some studies suggest that initiating CPAP at the time of identification of SDB is associated with improved maternal and fetal outcomes. For example, a study by Blyton et al. randomized 24 women with severe preeclampsia and 15 control nulliparous subjects to receive CPAP or no treatment, and showed that CPAP minimized the reduction of nocturnal cardiac output that is associated with preeclampsia [22]. Another study showed early use of CPAP in pregnant women with hypertension and chronic snoring was associated with better blood pressure control and improved pregnancy outcomes [23]. Finally, in a study that compared 14 pregnant women with OSA and treated with CPAP, to 31 women with OSA who were untreated, and 48 women without OSA, untreated maternal OSA was associated with significant impairment in fetal growth and slowing of fetal growth in the third trimester when compared with controls, but fetal growth did not differ between controls and women who were treated with CPAP during pregnancy [24]. Notably, compliance to CPAP therapy (and assignment to the CPAP treatment group) in this study was defined as at least 4 h of use for at least 4 nights/week. Data on compliance to CPAP in expectant and new mothers are very scarce.

Other treatment options such as oral appliance therapy and surgery can be considered when CPAP is not tolerated or is contraindicated, though the low likelihood of timely therapy in pregnancy makes these options less attractive. Mandibular advancement oral appliances help stabilize the mandible and reduce the frequency of respiratory events [10]. Surgeries such as uvulopalatopharyngoplasty are not recommended due to lower success rates compared to CPAP and risks associated with surgery during pregnancy [4].

There is also a role for behavioral modification and nonprescription approaches. Women with predisposing risk factors for SDB should receive counseling on controlling pregnancy weight gain, treating nasal congestion, and maintaining good sleep hygiene measures [4]. Positioning belts or pillows can also help promote sleep, especially for pregnant women with position-dependent SDB [4]. The left lateral position improves cardiac output and improves oxygen content [10].

There are no pharmacologic interventions to treat SDB at this time. However, emerging literature suggests a role for progesterone as a respiratory stimulant to lower SDB in pregnant women [11].

Clinical Pearls

- Sleep apnea prevalence in pregnancy is increasing due to higher rates of obesity and older maternal age.
- Changes in respiratory physiology, anatomy, endocrinology have both predisposing and protective effect on sleep-disordered breathing in pregnancy.
- Diagnosing OSA in pregnancy can be challenging; respiratory physiology is different during pregnancy, and home sleep testing can underestimate sleep apnea due to sleep disturbances that are common among pregnant women.
- Sleep disordered breathing in pregnancy poses risk of developing gestational hypertensive disorders, gestational diabetes, as well as low birthweight, preterm delivery and small for gestational age.
- Positive airway pressure (i.e., CPAP) is the most common treatment for OSA in pregnancy, but more studies are needed to better understand efficacy of this therapy for symptom improvement and risk reduction.
- Future implementation research should include the patient perspective and examine adherence to CPAP in the perinatal period with the goal of achieving optimal benefit for pregnant women with SDB and their infants.

References

1. Bobrowski RA. Pulmonary physiology in pregnancy. Clin Obstet Gynecol. 2010;53(2):285–300.
2. Bourjeily G, Fung JY, Sharkey KM, Walia P, Kao M, Moore R, et al. Airflow limitations in pregnant women suspected of sleep-disordered breathing. Sleep Med. 2014;15(5):550–5.
3. Oyiengo D, Louis M, Hott B, Bourjeily G. Sleep disorders in pregnancy. Clin Chest Med. 2014;35(3):571–87.
4. Ayyar L, Shaib F, Guntupalli K. Sleep-disordered breathing in pregnancy. Sleep Med Clin. 2018;13(3):349–57.
5. Facco FL, Ouyang DW, Zee PC, Grobman WA. Sleep disordered breathing in a high-risk cohort prevalence and severity across pregnancy. Am J Perinatol. 2014;31(10):899–904.
6. Maislin G, Pack AI, Kribbs NB, Smith PL, Schwartz AR, Kline LR, et al. A survey screen for prediction of apnea. Sleep. 1995;18(3):158–66.

7. Bourjeily G, Raker CA, Chalhoub M, Miller MA. Pregnancy and fetal outcomes of symptoms of sleep-disordered breathing. Eur Respir J. 2010;36(4):849–55.
8. Louis JM, Mogos MF, Salemi JL, Redline S, Salihu HM. Obstructive sleep apnea and severe maternal-infant morbidity/mortality in the United States, 1998-2009. Sleep. 2014;37(5):843–9.
9. Facco FL, Parker CB, Reddy UM, Silver RM, Koch MA, Louis JM, et al. Association between sleep-disordered breathing and hypertensive disorders of pregnancy and gestational diabetes mellitus. Obstet Gynecol. 2017;129(1):31–41.
10. Bourjeily G, Ankner G, Mohsenin V. Sleep-disordered breathing in pregnancy. Clin Chest Med. 2011;32(1):175–89, x.
11. Lee J, Eklund EE, Lambert-Messerlian G, Palomaki GE, Butterfield K, Curran P, et al. Serum progesterone levels in pregnant women with obstructive sleep apnea: a case control study. J Womens Health (Larchmt). 2017;26(3):259–65.
12. Popovic RM, White DP. Upper airway muscle activity in normal women: influence of hormonal status. J Appl Physiol (1985). 1998;84(3):1055–62.
13. Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2017;13(3):479–504.
14. Dominguez JE, Street L, Louis J. Management of obstructive sleep apnea in pregnancy. Obstet Gynecol Clin N Am. 2018;45(2):233–47.
15. Bourjeily G, Danilack VA, Bublitz MH, Lipkind H, Muri J, Caldwell D, et al. Obstructive sleep apnea in pregnancy is associated with adverse maternal outcomes: a national cohort. Sleep Med. 2017;38:50–7.
16. Bublitz MH, Carpenter M, Amin S, Okun ML, Millman R, De La Monte SM, et al. The role of inflammation in the association between gestational diabetes and obstructive sleep apnea: a pilot study. Obstet Med. 2018;11(4):186–91.
17. Louis J, Auckley D, Miladinovic B, Shepherd A, Mencin P, Kumar D, et al. Perinatal outcomes associated with obstructive sleep apnea in obese pregnant women. Obstet Gynecol. 2012;120(5):1085–92.
18. O'Brien LM, Bullough AS, Owusu JT, Tremblay KA, Brincat CA, Chames MC, et al. Pregnancy-onset habitual snoring, gestational hypertension, and preeclampsia: prospective cohort study. Am J Obstet Gynecol. 2012;207(6):487 e1–9.
19. Franklin KA, Holmgren PA, Jonsson F, Poromaa N, Stenlund H, Svanborg E. Snoring, pregnancy-induced hypertension, and growth retardation of the fetus. Chest. 2000;117(1):137–41.
20. Chen YH, Kang JH, Lin CC, Wang IT, Keller JJ, Lin HC. Obstructive sleep apnea and the risk of adverse pregnancy outcomes. Am J Obstet Gynecol. 2012;206(2):136 e1–5.
21. Pengo MF, Banerjee D, Kaur A, Bourjeily G. Sleep disordered breathing in pregnancy: food for thought. Obstet Med. 2016;9(4):153–5.
22. Blyton DM, Sullivan CE, Edwards N. Reduced nocturnal cardiac output associated with pre-eclampsia is minimized with the use of nocturnal nasal CPAP. Sleep. 2004;27(1):79–84.
23. Poyares D, Guilleminault C, Hachul H, Fujita L, Takaoka S, Tufik S, et al. Pre-eclampsia and nasal CPAP: part 2. Hypertension during pregnancy, chronic snoring, and early nasal CPAP intervention. Sleep Med. 2007;9(1):15–21.
24. Kneitel AW, Treadwell MC, O'Brien LM. Effects of maternal obstructive sleep apnea on fetal growth: a case-control study. J Perinatol. 2018;38(8):982–8.

Chapter 11
Obesity Hypoventilation Syndrome

Aditya Chada, Faisal Zahiruddin, and Nancy Collop

Case

AS was a 54-year-old man referred from the bariatric clinic for evaluation of possible sleep apnea noting snoring and excessive sleepiness (Epworth Sleepiness Scale score 13/24). At the time of his referral, his BMI was 68.1 kg/m^2. His medical history included hypertension and chronic venous stasis; he had not had any recent hospitalizations. His only medication was a combination anti-hypertensive: hydrochlorothiazide/lisinopril. On physical examination, his awake oxygen saturation was 93%, his blood pressure was 123/78 mm Hg. His physical examination was remarkable for a very large neck (circumference 23 inches); a modified Mallampati score of 4 and brawny lower extremity edema. His serum bicarbonate level was 29 mmol/L; thyroid function tests were normal.

The polysomnography showed severe obstructive sleep apnea during the first 3 h of the study (apnea hypopnea index (AHI) 117 events/h) with oxygen saturation to as low as 74%. No REM sleep was observed during the baseline portion (Table 11.1). Due to the severity of the sleep apnea, CPAP and bilevel PAP were used. CPAP was ineffective at controlling breathing events with pressures as high as 19 cm H_2O. Bilevel PAP resulted in lower AHI's however events and oxygenation during REM sleep were suboptimally controlled.

A. Chada · N. Collop (✉)
Emory University, Atlanta, GA, USA
e-mail: nancy.collop@emory.edu

F. Zahiruddin
Emory University, Atlanta, GA, USA

Pulmonary, Critical Care, and Sleep Medicine, Houston Methodist Hospital, Houston, TX, USA
e-mail: fzahiruddin@houstonmethodist.org

C. Won (ed.), *Complex Sleep Breathing Disorders*,
https://doi.org/10.1007/978-3-030-57942-5_11

Table 11.1 Polysomnography results

Baseline data	
Total sleep time (min)	165 min
Sleep efficiency (TST/TRT)	96.6%
N1 (% TST)	2.4%
N2 (% TST)	97.6%
N3 (% TST)	0
REM (% TST)	0
Apnea hypopnea index (events/hr. TST)	117
Nadir SpO_2	74%
Hypoxic burden (% of time $SpO_2 < 90\%$)	45.7%
PAP data	
Total sleep time (min)	275 min
Sleep efficiency (TST/TRT)	98.6%
N1 (% TST)	2.4%
N2 (% TST)	81.1%
N3 (% TST)	4.5%
REM (% TST)	12%
Final bilevel PAP	18/14 cm H_2O
AHI on final bilevel PAP	9.8

TST total sleep time, *TRT* total recording time, *N1* stage NREM 1, *N2* stage NREM 2, *N3* stage NREM 3, *REM* stage REM, *SpO_2* Oxygen saturation measured by pulse oximetry, *AHI* apnea hypopnea index

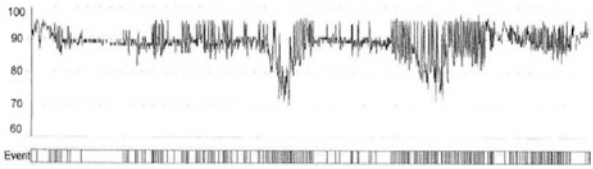


Fig. 11.1 Overnight oximetry performed while on bilevel PAP therapy

He was started on bilevel PAP therapy (18/14 cm H_2O) and returned to the sleep clinic after a month. An arterial blood gas was obtained during wake: pH 7.39, $PaCO_2$ 49 mm Hg, PaO_2 64 mm Hg. Due to the suboptimal titration, an overnight oximetry was performed while wearing his bilevel PAP device (Fig. 11.1). It showed intermittent desaturations with persistent low oxygen saturation at times.

A full night titration study was subsequently performed utilizing transcutaneous carbon dioxide monitoring ($TcCO_2$). The patient slept very poorly during the study. It was noted that even on PAP therapy, his $TcCO_2$ levels rose into the mid 50's. Unfortunately, no REM sleep was again noted during the titration. The bilevel settings were changed to increase the amount of pressure support (bilevel PAP settings changed from 18/14 cm H_2O to 22/11 cm H_2O).

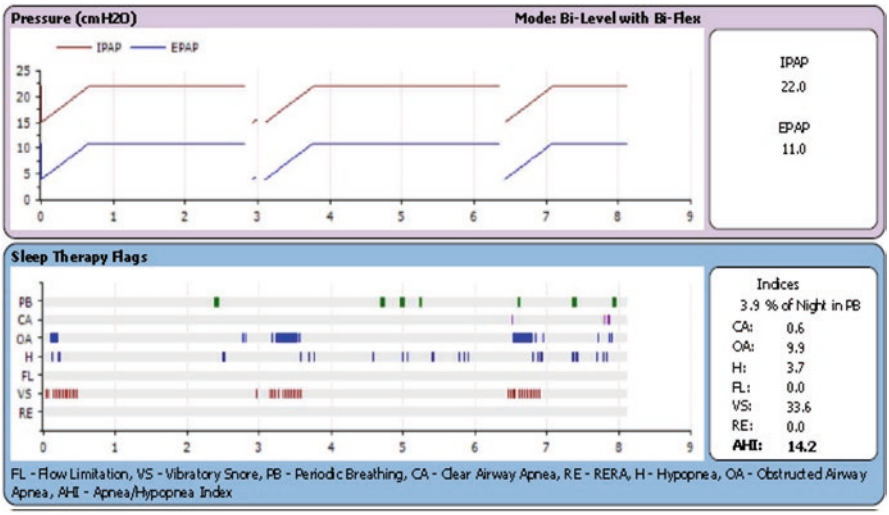


Fig. 11.2 Single night download from PAP device showing frequent breathing events while device is ramping. Legend: Top panel is pressure settings; Bottom panel are sleep disordered breathing events detected by PAP device. PB periodic breathing, CA clear airway apnea, OA obstructive apnea, H hypopnea, FL flow limited breathing, VS vibratory snoring, RE RERA index, AHI apnea hypopnea index

The bariatric clinic mandated that the patient get his weight under 400 lbs prior to being considered a candidate for surgery. He continued to use his bilevel PAP device nightly and returned for a clinic visit on the new settings after 6 months. It was noted that the AHI was still elevated AHI on download = 9.5) on the settings of 22/11 cm H_2O. Review of the nightly download data showed that at the beginning of the night and during awakenings, he was using the ramping feature and frequent respiratory events occurred while the pressure was slowly rising over 40 min (Fig. 11.2). The ramp was subsequently turned off and at the next visit, the AHI from the downloaded data was reduced to <5 events/h. Repeat overnight oximetry showed that on the new settings, oxygen saturation was now remaining >90%. Similarly, his Epworth Sleepiness Scale score was now 3/24. Unfortunately, despite working on diet, he was unable to reduce his weight to <400 lbs, and bariatric surgery remained on hold.

Discussion

Obesity Hypoventilation Syndrome (OHS) is a breathing disorder in obese people that is characterized by sleep-related breathing disorder and hypoventilation during wakefulness. Many people with this condition frequently have severe obstructive sleep apnea (OSA) with significant sleep-related hypoxemia. The risk of OHS increases as BMI increases, and sleep clinicians are increasingly challenged with

these patients as the rate of severe obesity continues to rise sharply in the USA and worldwide. Obesity hypoventilation syndrome is important to diagnosis and treat given the significant morbidity and mortality associated with it [1, 2].

Epidemiology

The exact prevalence of OHS is unknown. One study estimated the prevalence of OHS in the adult US population to be 0.15–0.3% [5]. This estimate was based on the prevalence of severe obesity [BMI >40 kg/m^2] in the United States of 3.0%, with the assumption that half of severely obese patients have OSA, and 10–20% of those with OSA have OHS. More recently, in 2010, the prevalence of obesity was found to be increased to 6% of the general US adult population; making a more recent estimated prevalence of OHS roughly 0.6% (i.e. approximately 1 in 160 adults in the USA) [3, 4]. Clinical predictors of OHS include BMI >35 kg/m^2, $PaCO_2$/BMI <1.5, resting awake $SaO_2 < 91\%$, smoking, and female sex [5].

Definition

Obesity hypoventilation syndrome is defined as the combination of obesity (body mass index [BMI] above 30 kg/m^2) and hypercapnia ($PaCO_2$ above 45 mm Hg) during wake with sleep-disordered breathing, after excluding other causes of hypoventilation, such as central hypoventilation syndromes, neuromuscular diseases, severe hypothyroidism, restrictive chest wall deformities, or severe obstructive pulmonary disorders [6].

Intermittent partial (hypopnea) or complete (apnea) upper airway collapse that leads to recurring episodes of hypoxemia and hypercapnia, sleep fragmentation, and increased sympathetic activity are the characteristic features of OHS [5]. Hypoxemia during sleep can lead to constriction of pulmonary arteries which can lead to strain on the right side of the heart and to right sided heart failure (i.e., cor pulmonale) [7].

Pathophysiology

OHS is a consequence of interplay of various process, such as sleep-related breathing disorders, altered ventilatory control, excessive respiratory load, and functional respiratory impairment [8].

(a) Excessive Load on Respiratory System

Excessive load on the respiratory system can lead to alterations of respiratory mechanics, ineffectiveness of respiratory muscles, and a blunted respiratory drive.

Alterations of Respiratory Mechanics Decreased pulmonary distensibility in obese patients can cause decreased ventilation of the lower lung lobes, which can lead to alterations in ventilation-perfusion, resulting in hypoxemia. Alveoli can close before end expiration which leads to decreased tidal volume and increased respiratory rate, which in turn can cause increased dead space ventilation. In patients with OHS, a decreased residual functional capacity, expiratory reserve volume, and total lung capacity can be observed [9, 10].

Weakness of Respiratory Muscles Effectiveness of respiratory muscles is worsened when supine. Adipose tissue restricts the movement of muscles which can increase the work the breathing. This reduces chest wall compliance and may lead to reduced total lung capacity. Increased respiratory effort in these patients is required for effective ventilation [11, 12].

Blunted Respiratory Drive Normally, when central chemoreceptors detect an increase in $PaCO_2$, there is an increase in ventilatory drive; however, this respiratory response is blunted in OHS. This is attributed to several reasons including leptin resistance, sleep-disordered breathing, and genetic predisposition. Leptin is secreted by adipose tissue and stimulates ventilation and regulates appetite. Obese patients have higher levels of this hormone. Researchers have studied genetically altered obese mice who were deficient in leptin. The mice had decreased ventilatory response capacity and had hypercapnia when awake (despite the increased ventilation in response to increased production of CO_2) [13, 14].

(b) Sleep-Disordered Breathing

Obstructive Sleep Apnea Obstructive sleep apnea is observed in 90% of OHS patients and was notably severe in our case. Elevated $PaCO_2$ is due to metabolic production of CO_2 and disrupted ventilation during apneic episodes. Normally, patients are able to increase CO_2 clearance by compensatory increases in ventilation. However, this is disrupted in OHS patients which leads to build up of CO_2. In response to hypercapnia, the renal system lowers bicarbonate clearance to compensate for the acidity. As this continues, bicarbonate builds up during the night. This further blunts the ventilatory response to increased carbon dioxide which leads to a vicious cycle of persistent hypercapnia [15].

Sleep Hypoventilation It is estimated that 5–10% of patients with OHS have sleep hypoventilation and a $PaCO_2$ elevation during sleep of 10 mmHg or higher. This is often exacerbated during stage REM sleep due to muscle atonia and further reduced carbon dioxide responsiveness. These patients are clinically indistinguishable from patients with coexisting obstructive sleep apnea. Sustained hypoxia during sleep is a neurocognitive depressant, which can delay arousal and worsen hypoventilation. Studies have shown that hypercapnic patients have lower mean overnight pulse oximetric saturations [16]. While most sleep laboratories do not use transcutaneous CO_2 ($TcCO_2$) sensors, they can be very helpful in determining if CO_2 levels are increased. In our patient, while his daytime CO_2 was only mildly elevated, there was a significant increase in $TcCO_2$ levels during sleep consistent with hypoventilation.

Diagnosis

The definitive test for hypoventilation is an arterial blood gas performed on room air during wakefulness. By definition the arterial blood gas in hypoventilation demonstrates hypercapnia, hypoxemia, and a relatively normal alveolar-arterial gradient. The alveolar-arterial gradient in OHS may not be completely normal, however, because of obesity-related atelectasis or pulmonary hypertension. A low threshold for pulmonary function testing and chest imaging should be considered to exclude other causes of hypercapnia. In OHS, pulmonary function tests can be normal but typically reveal a mild to moderate restrictive defect due to body habitus and significant reduction in expiratory reserve volume. Patients with OHS may also have mild reductions in maximal expiratory and inspiratory pressures related to the combination of abnormal respiratory mechanics. Significant deficits should prompt workup for neuromuscular disease. While some degree of reduction in forced expiratory volume in 1 s (FEV1) may be seen with obesity, a significant obstructive ventilatory defect should prompt consideration of other hypercapnic pulmonary disorders such as COPD, asthma, or bronchiectasis. Chest imaging excludes other etiologies of hypoxemia and is generally expected to be unremarkable in OHS with the exception of perhaps mild basilar atelectasis.

Diagnosis of OHS is quite difficult unless clinicians have a high index of suspicion, as arterial blood gases are not routinely performed in sleep clinics and laboratories [17]. Currently, there are no guidelines about correct and cost-effective methods for screening or diagnosing OHS [18]. We recommend respiratory and sleep evaluation for all patients undergoing bariatric surgery which includes arterial blood gas assessment for those with BMI >50 kg/m^2 [19] because of high prevalence of postoperative respiratory complications in this group of patients.

Pulse oximetry and serum bicarbonate levels can be used as screening tools before employing a confirmatory arterial blood gas. OHS should be suspected in obese individuals with sleep disordered breathing, with venous blood bicarbonate levels >27 mEq/L. This has shown to be 92% sensitive, though only 50% specific, for daytime hypercapnia in suspected OHS patients [20]. Indeed, in our patient, serum bicarbonate was elevated (29 mmol/L). Often confounding is that obese patients often have comorbid cardiovascular disease and are taking loop diuretics, which may increase serum bicarbonate levels without concomitant hypoventilation. Similarly, a resting awake pulse oximetry level < 94% in obese individuals with sleep disordered breathing should prompt further workup with an arterial blood gas to investigate the possibility of OHS [25].

Management

(a) *Continuous positive airway pressure and noninvasive mechanical ventilation*

In patients with concurrent obstructive sleep apnea-hypopnea syndrome, nocturnal continuous positive airway pressure therapy is usually effective. This therapy provides

continuous positive pressure during the respiratory cycle, which maintains upper airway patency, eliminates apneas and hypopneas, and restores daytime eucapnia [21].

Noninvasive mechanical ventilation can be achieved with a nasal or full face mask and either a bilevel positive airway pressure device (with or without a backup respiratory rate), a volume-targeted bilevel pressure device, or a home ventilator. Bilevel systems (i.e., NIV) have an advantage over CPAP of permitting independent adjustment of inspiratory and expiratory positive airway pressure [26]. The bilevel settings are titrated in a way that the lower pressure (EPAP) is set to improve the increased work of breathing related to upper airway obstruction during sleep and by increasing lung volumes by recruiting the atelectatic lung, while the higher inspiratory pressure (IPAP) is set to overcome the work of breathing due to reduced chest wall compliance in severe obesity and correct hypercapnia by increasing tidal volume and ventilation [23].

Noninvasive ventilation (NIV) is not necessarily superior to CPAP since relieving the upper airway obstruction during sleep (corrected by both CPAP and bilevel PAP) is one of the important determinants of treatment response [23]. The recent American Thoracic Society Clinical Practice Guideline recommends starting with CPAP therapy for stable ambulatory patients with severe OSA (AHI $\geq$ 30 events/h) [24]. The Guideline suggests NIV therapy should be initiated upon discharge in hospitalized patients with respiratory failure suspected of having OHS, until they are able to undergo further sleep testing. In OHS patients, it is necessary to monitor parameters during sleep such as mask flow, air leak, exhaled tidal volume, delivered pressure, and triggered backup mechanical breaths using polysomnography. Switching to NIV can be done if $PaCO_2$ doesn't come to normal despite CPAP for 3 months. Once bilevel therapy is initiated they need close follow up in order to monitor their daytime symptoms along with ABG and/or serum bicarb in some cases. Patients are continued on the same settings once subjective and objective evidence of improvement are noted. Even after adequate titration with CPAP, nearly 4 out of 10 patients require supplemental oxygen according to studies, whereas it is approximately 1 in 10 with adequate NIV [22]. In our case, CPAP alone was ineffective in managing the hypoventilation noted during REM and in fact a higher level of pressure support was needed to ultimately attain adequate ventilation during sleep.

(b) *Avoiding Management Errors*

Supplementing oxygen is not of great value in patients with OHS as administration of supplemental oxygen leads to reversal of hypoxic vasoconstriction and redistribution of blood flow to the poorly ventilated alveoli, which leads to an increase in dead space fraction, ultimately leading to hypercapnia. Patients with OHS are highly sensitive to added oxygen. There can be a 3–10 mm Hg increase in $PaCo_2$ with 50–100% of fraction of inspired oxygen. Hence, it is recommended that oxygen should be titrated to keep peripheral capillary oxygen saturations between 89% and 92% [23].

(c) *Surgery and Perioperative Management*

Bariatric surgery is the most effective approach to achieving and maintaining more substantial degrees of weight loss over longer periods however few studies have specifically looked at outcomes in patients with OHS. Bariatric surgery has been recommended as a treatment for OSA patients with a BMI > 30 kg/m^2, and it has been shown to improve nocturnal oxygenation in OSA patients in one meta-analysis [25]. However another meta-analysis found that the apnea-hypopnea index remained high in many individuals, and this may lead to problems as the presence of persisting sleep-disordered breathing is often not recognized, and patients perceive their sleep symptoms have resolved and therefore may discontinue therapy prematurely after surgery [26].

The surgical approach to weight loss is being increasingly used in severely morbidly obese (BMI > 50 kg/m^2) individuals. Although significant and sustained weight loss in these groups has been reported, few achieve a reduction in BMI < 40 kg/m^2. In our patient, the bariatric surgeons would not attempt surgery until BMI was in a less than severely morbidly obese range.

Providing anesthesia during surgery can be challenging in OHS patients. Anesthesia should be given to OHS patients in ramp position, i.e., torso tilted with head elevation by 25° to improve the glottis view while intubating thus preventing atelectasis [27]. To avoid postoperative complications and for better airway and oxygen maintenance, patient should be positioned in semi-upright or lateral position. Rapid emergence from anesthesia is recommended, and tracheal extubation should only be performed after the patient becomes fully conscious. Opioid-sparing analgesic is used to avoid opioid-induced ventilator improvement [28].

Clinical Pearls

- As the obesity burden is scaling exponentially, OHS prevalence is also expected to increase.
- Timely diagnosis and treatment are key elements in reducing morbidity and mortality associated with the disease. The criteria for OHS diagnosis include the presence of sleep disordered breathing (e.g., OSA or sleep-related hypoventilation), and daytime alveolar hypoventilation (arterial $PCO_2 > 45$ mm Hg) among patients with BMI ≥30 kg/m^2 in the absence of other causes of hypoventilation.
- Pulse oximetry ($SpO_2 < 94\%$) and serum bicarbonate (>27 mmol/L) can be used as screening tools which will aid in improving diagnosis.
- Successful management of OHS consists of positive airway pressure therapy with close follow-up to assure adequate reduction in sleep disordered breathing and hypoventilation; judicious use of supplemental oxygen; and weight management which may include consideration of bariatric surgery.
- CPAP is recommended for stable ambulatory patients with severe OSA. NIV may be considered if patients fail CPAP (e.g., $PaCO_2$ remains elevated

despite CPAP use). NIV is also recommended for home use in patients hospitalized with acute hypercapnic respiratory failure and suspected OHS, until sleep testing is able to be performed.

- The Bilevel settings are titrated in a way that the lower pressure (EPAP) is set to improve the increased work of breathing related to upper airway obstruction during sleep and by increasing lung volumes by recruiting the atelectatic lung while the higher inspiratory pressure (IPAP) is set to overcome the work of breathing due to reduced chest wall compliance in severe obesity and correct hypercapnia by increasing tidal volume.

References

1. Berg G, Delaive K, Manfreda J, et al. The use of health-care resources in obesity-hypoventilation syndrome. Chest. 2001;120:377–83.
2. Nowbar S, Burkhart KM, Gonzales R, et al. Obesity associated hypoventilation in hospitalized patients (prevalence, impact, and outcome). Am J Med. 2004;116:1–7.
3. Flegal KM, Carroll MD, Kit BK, et al. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. JAMA. 2012;307(5):491.
4. Balachandran JS, Masa JF, Mokhlesi B. Obesity hypoventilation syndrome epidemiology and diagnosis. Sleep Med Clin. 2014;9(3):341–7.
5. Bülbül Y, Ayik S, Ozlu T, Orem A. Frequency and predictors of obesity hypoventilation in hospitalized patients at a tertiary health care institution. Ann Thorac Med. 2014;9(2):87–91.
6. Littleton SW, Mokhlesi B. The Pickwickian syndrome - obesity hypoventilation syndrome. Clin Chest Med. 2009;30(3):467–78.
7. Kessler R, Chaouat A, Weitzenblum E, et al. Pulmonary hypertension in the obstructive sleep apnea syndrome (prevalence, causes, and therapeutic consequences). Eur Respir J. 1996;9:787–94.
8. Manuel ARG, Hart N, Stradling JR. Is a raised bicarbonate, without hypercapnia, part of the physiologic spectrum of obesity-related hypoventilation? Chest. 2015;147(2):362–8.
9. Mortimore IL, Marshall I, Wraith PK, et al. Neck and total body fat deposition in nonobese and obese patients with sleep apnea compared with that in control subjects. Am J Respir Crit Care Med. 1998;157(1):280–3.
10. Nairnark A, Cherniack RM. Compliance of the respiratory system and its components in health and obesity. J Appl Physiol. 1960;15:377–82.
11. Lin CK, Lin CC. Work of breathing and respiratory drive in obesity. Respirology. 2012;17(3):402–11.
12. Piper AJ, Yee BJ. Hypoventilation syndromes. Compr Physiol. 2014;4(4):1639–76.
13. Tankersley CG, O'Donnell C, Daood MJ, et al. Leptin attenuates respiratory complications associated with the obese phenotype. J Appl Physiol. 1998;85(6):2261–9.
14. Phipps PR, Starritt E, Caterson I, et al. Association of serum leptin with hypoventilation in human obesity. Thorax. 2002;57(1):75–6.
15. Pierce AM, Brown LK. Obesity hypoventilation syndrome: current theories of pathogenesis. Curr Opin Pulm Med. 2015;21(6):557–62.
16. Norman RG, Goldring RM, Clain JM, et al. Transition from acute to chronic hypercapnia in patients with periodic breathing: predictions from a computer model. J Appl Physiol. 2006;100(5):1733–41.

17. Piper AJ, Grunstein RR. Obesity hypoventilation syndrome—mechanisms and management. Am J Respir Crit Care Med. 2011;183(3):292–8.
18. Mokhlesi B, Tulaimat A. Recent advances in obesity hypoventilation syndrome. Chest. 2007;132(4):1322–36.
19. Mechanick JI, Kushner RF, Sugerman HJ, et al. American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery medical guidelines for clinical practice for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient. Obesity (Silver Spring). 2009;17:S1–S70.
20. Mokhlesi B, Tulaimat A, Faibussowitsch I, Wang Y, Evans A. Obesity hypoventilation syndrome: prevalence and predictors in patients with obstructive sleep apnea. Sleep Breath. 2007;11:117–24.
21. Piper AJ, Sullivan CE. Effects of short-term NIPPV in the treatment of patients with severe obstructive sleep apnea and hypercapnia. Chest. 1994;105:434–40.
22. Hollier CA, Harmer AR, Maxwell LJ, et al. Moderate concentrations of supplemental oxygen worsen hypercapnia in obesity hypoventilation syndrome: a randomised crossover study. Thorax. 2014;69(4):346–53.
23. Wijesinghe M, Williams M, Perrin K, et al. The effect of supplemental oxygen on hypercapnia in subjects with obesity-associated hypoventilation: a randomized crossover clinical study. Chest. 2011;139(5):1018–24.
24. Mokhlesi, Masa, Brozek et al. Evaluation and Management of Obesity Hypoventilation Syndrome. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2019;200(3):e6–24.
25. Zhang Y, Wang W, Yang C, Shen J, Shi M, Wang B. Improvement in nocturnal hypoxemia in obese patients with obstructive sleep apnea after bariatric surgery: a meta-analysis. Obes Surg. 2018;29:601–8. [epub ahead of print].
26. Greenburg DL, Lettieri CJ, Eliasson AH. Effects of surgical weight loss on measures of obstructive sleep apnea: a meta-analysis. Am J Med. 2009;122:535–42.
27. Gupta A, Stierer T, Zuckerman R, et al. Comparison of recovery profile after ambulatory anesthesia with propofol, isoflurane, sevoflurane and desflurane: a systematic review. Anesth Analg. 2004;98(3):632–41.
28. Lftikhar IH, Roland J. Obesity hypoventilation syndrome. Clin Chest Med. 2018;39(2):427–36.

Chapter 12
Sleep Breathing Disorders in Amyotrophic Lateral Sclerosis

Lisa Wolfe and Ashima Sahni

Case

A 65-year-old male presented to the pulmonary/sleep clinic for a second opinion after developing difficulty tolerating his new home mechanical ventilator with mask interface. The patient was diagnosed at an outside facility with limb onset amyotrophic lateral sclerosis (ALS) 6 months ago. At that time, the patient was experiencing difficulties with his sleep. He was unable to sleep on his back due to dyspnea and a choking sensation. His sleep was disturbed by vivid dreams along with morning headaches. Approximately 2 months ago, in-office spirometry showed an upright forced vital capacity (FVC) of 45% predicted.

Due to these complaints and findings, home-based noninvasive ventilation was initiated using a bilevel positive airway pressure in the spontaneous-timed (bilevel PAP-ST) mode with a backup respiratory rate (in this case, a VPAP-ST™ ResMed). The nighttime symptoms subsided with the use of the device. The download from bilevel PAP-ST device showed excellent compliance with minimum leak (Table 12.1). Since the patient seemed to benefit from therapy and was living in a location where the electricity was unpredictable due to a high number of hurricanes, his physician decided to switch his current device to a home mechanical ventilator with internal battery and power alarms (in this case, a Trilogy™ Philips Respironics). He could not use the new device for more than one night due to difficulty in breathing and came to us for a second opinion. The 1-day download from the device showed that all the breaths were triggered by the patient (Table 12.2). At the time, he presented for a second opinion, and the patient denied any shortness of breath on exertion, though the patient's physical activity was limited. He was having more

L. Wolfe (✉) · A. Sahni
Northwestern Memorial, Department of Medicine, Chicago, IL, USA
e-mail: lwolfe@northwestern.edu

C. Won (ed.), *Complex Sleep Breathing Disorders*,
https://doi.org/10.1007/978-3-030-57942-5_12

Table 12.1 Download data showing bilevel PAP-ST settings and compliance

Bi-PAP settings	
Mode	*Spontaneous/timed*
IPAP set (cmH_2O)	13
EPAP set (cmH_2O)	7
Set bilevel backup rate BPM	13
Ti minimum time (s)	1.5
Ti maximum time (s)	2.5
Trigger	Very high
Cycle	Very low
Rise time (ms)	500
Bi-PAP download	
Leak median	0.2 LPM
Events/h	2
Nights used	100%
Avg sleep time	9 h
Avg exhaled Vt	289 mL
Avg RR total	16 BPM
Avg MV	4.8 LPM

Bi-PAP bilevel positive airway pressure, *IPAP* inspiratory positive airway pressure, *EPAP* expiratory positive airway pressure, *cmH_2O* centimeters of water pressure, *BPM* breaths per minute, *Ti* inspiratory time, *s* seconds, *ms* milliseconds, *LPM* liters per minute, *Vt* tidal volume, *RR* respiratory rate, *MV* minute ventilation, *Avg* average, *mL* milliliters

bulbar weakness, and his speech was more difficult to understand. He uses a cough assist device as needed.

The patient is a nonsmoker with no other medical history except ALS. On physical examination, his BMI was 30 kg/m^2, heart rate 80 beats/min, and respiratory rate 20 breaths/min. Patient had tongue fasciculations. There were decreased breath sounds bilaterally with atrophy of the bilateral lower limbs and reduced reflexes bilaterally in the lower limbs. Spirometry was performed which showed reduced forced vital capacity along with palatal vibrations (Fig. 12.1).

In-office titration was performed on his ventilator (Trilogy™ Philips Respironics). The ventilator was changed from bilevel ST mode to pressure-controlled ventilation (see Table 12.3 for settings). The patient felt comfortable on these settings and went home with the plan of doing overnight pulse oximetry on the current setting. The overnight pulse oximetry showed no significant desaturations, and the patient felt better on the current settings (Fig. 12.2). At this time, the secondary settings were added to the ventilator to assist the patient with mouthpiece ventilation (i.e., sip ventilation).

Table 12.2 Download data from the patient's mechanical ventilator (Trilogy™ Philips Respironics)

NIV settings	
Mode	*Spontaneous/timed*
IPAP set (cmH_2O)	13
EPAP set (cmH_2O)	7
Set bilevel backup rate BPM	13
Ti time (s)	1.5
Trigger/cycle	Auto Trak
Rise time	3
NIV download	
Leak median	32 LPM
Events/h	NA
Nights used	1
Avg sleep time	54 min
Avg exhaled Vt	287 mL
Avg RR total	23 BPM
Avg MV	6.43 LPM

NIV noninvasive ventilation, *IPAP* inspiratory positive airway pressure, *EPAP* expiratory positive airway pressure, *cmH_2O* centimeters of water pressure, *BPM* breaths per minute, *Ti* inspiratory time, *s* seconds, *LPM* liters per minute, *Vt* tidal volume, *RR* respiratory rate, *MV* minute ventilation, *Avg* average, *mL* milliliters

Note the respiratory rate was faster than the backup rate, suggesting all breaths were spontaneous breaths

Discussion

Amyotrophic lateral sclerosis is an incurable neurodegenerative disorder that causes upper and lower motor neuronal degeneration. It is also known as Lou Gehrig's disease and was first described in the nineteenth century by Charcot. The annual incidence of ALS is 1–3 cases per 1,00,000 people worldwide. The peak incidence is in the seventh decade of life. Respiratory muscle weakness as an initial presentation is very rare (1–3%). Progressive neuromuscular respiratory failure is the most common cause of death in ALS patients.

This case highlights the clinical signs and symptoms of respiratory failure in patients with ALS [1] (Table 12.4). In our case, the patient presented with the symptoms of orthopnea, nightmares, and morning headaches. The other associated symptoms could include excessive sleepiness, early satiety due to muscle fatigue, confusion, or fragmented sleep.

In the past, tracheostomy with invasive ventilation was performed during the course, but with the advancement in technology, noninvasive ventilation has become the primary mode to assist with ventilation [2]. Based on the current guidelines, as highlighted in our case, ALS patients do not need to obtain an in-laboratory sleep

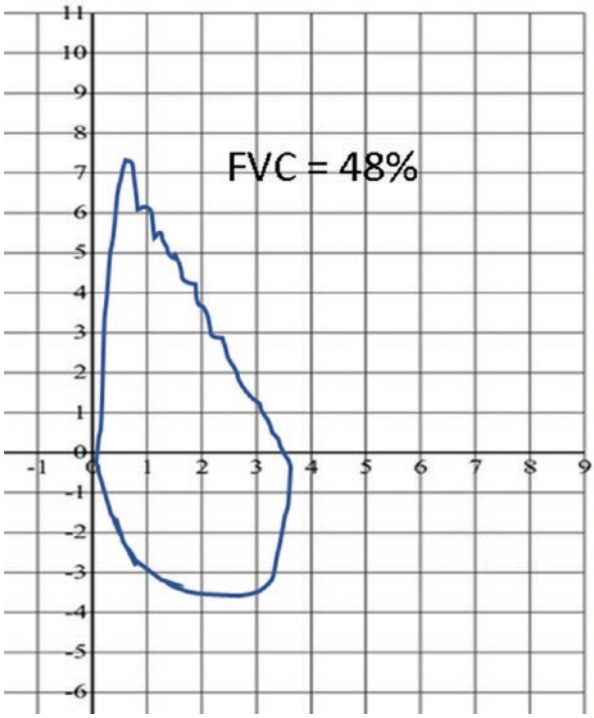


Fig. 12.1 Spirometry during the clinic visit showing reduced FVC and palatal vibrations. FVC forced vital capacity

Table 12.3 The following setting changes were made to the patient's Trilogy™ Philips Respironics

Mode	Pressure control
NIV titration	
IPAP set (cmH_2O)	14
EPAP set (cmH_2O)	7
Set bilevel backup rate BPM	13
Ti time (s)	1.5
Trigger/cycle	Flow trigger 2 LPM
Rise time	1
Exhaled Vt	300–400 mL

NIV noninvasive ventilation, *IPAP* inspiratory positive airway pressure, *EPAP* expiratory positive airway pressure, *cmH_2O* centimeters of water pressure, *BPM* breaths per minute, *Ti* inspiratory time, *s* seconds, *LPM* liters per minute, rise time ranges from 1 to 5 with 1 being fastest and 5 slowest rate, *Vt* tidal volume, *mL* milliliters

The ventilator's mode was changed from bilevel ST to pressure control ventilation

study for diagnostic purposes [1] (Table 12.5). Once they have signs and symptoms suggestive of hypoventilation (Table 12.4), either spirometry, overnight pulse oximetry, or an arterial blood gas is sufficient to qualify for initiation of noninvasive ventilation.

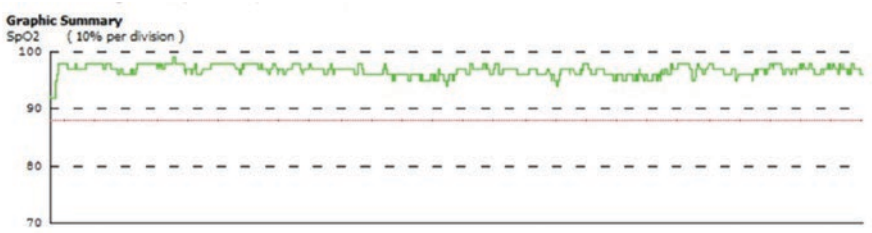


Fig. 12.2 An 8-hour overnight recording of pulse oximetry (SpO_2) on newer trilogy settings

Table 12.4 Signs and symptoms of respiratory failure in amyotrophic lateral sclerosis (ALS)

Respiratory signs and symptoms of ALS	
Symptoms	Signs
Dyspnea	Tachypnea
Nightmares	Tongue fasciculation
Headaches	Sleep-related hypoxemia
Ineffective cough	Awake or sleep-related hypoventilation
Early satiety	Weak sniff
Fatigue with eating	Thoraco-abdominal paradox
Daytime sleepiness	Quiet speech
Disturbed sleep	

Table 12.5 General insurance guidelines for qualifying for noninvasive ventilation

Qualifying criteria for non-invasive ventilator therapy in neuromuscular disease	
Bi-level PAP	Mechanical ventilation with mask
1. Symptoms of hypoventilation	1. Symptoms of hypoventilation
AND	AND
2. Any ONE of the following	2. Proof of medical necessity in an MD note
FVC < 50% predicted	
MIP < -60 cmH_2O	
$PaCO_2$ > 45 mmHg	
Pulse Ox < 88% for > 5 mins during an over night recording	

ALS amyotrophic lateral sclerosis, *PAP* positive airway pressure, *FVC* forced vital capacity, *MIP* maximal inspiratory pressure, *$PaCO_2$* arterial pressure of carbon dioxide, *Pulse Ox* oxygen saturation as measure by pulse oximetry, *MD* medical doctor
Note a sleep study is *not* required for positive airway pressure therapy in neuromuscular disease patients

The next important step is to decide which device to choose. In this patient, the physician initially chose a respiratory assist device (RAD) but then switched over to home mechanical ventilator (HMV) (Fig. 12.3). RAD devices are smaller than HMV, but they do not have alarm features or a backup battery, which becomes an important consideration in patients who live in places where the electricity is

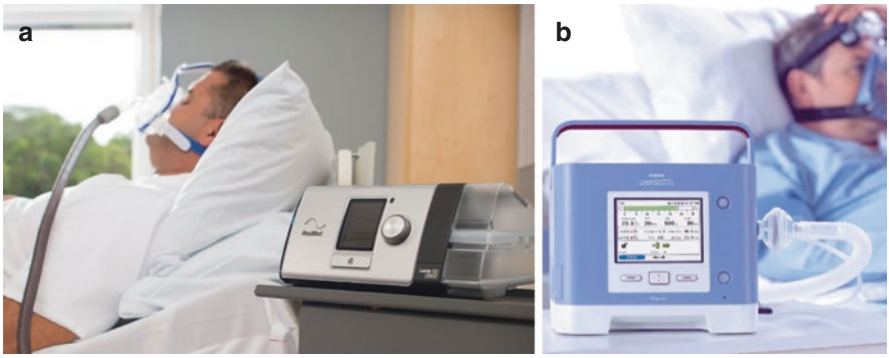


Fig. 12.3 Noninvasive positive pressure ventilation may be delivered by (**a**) respiratory assist device such as the ResMed VPAP-ST™ or (**b**) home mechanical ventilator such as the Respironics Trilogy™, both shown here. A respiratory assist device differs from a home mechanical ventilator by its lack of alarm features, lack of backup battery, and lack of more advance ventilator modes. Algorithms for pressure delivery differ between manufacturers and machine types, which may affect patient comfort and synchrony. Insurance coverage requirements for the two types of devices may also differ

unreliable or if portability is needed for daytime therapy such as mouthpiece ventilation (MPV). As the disease progresses, MPV or daytime mask ventilation becomes essential. This cannot be achieved with RAD devices. They do not offer essential features such as the MPV trigger, leak tolerance, expiratory positive airway pressure (EPAP) setting of 0 cmH_2O, or volume-cycled modes. HMVs have these capabilities. On the other hand, HMVs are more expensive and bulkier as compared to a RAD device.

The selection of mode and the deeper understanding of the various machines and modes of noninvasive ventilation is crucial to assist in the care of such patients. In our patient, he was switched from a VPAP-ST™ (ResMed) to Trilogy™ (Respironics) machine. On the initial glance, the settings on each machine look the same, but clearly there is a difference in the algorithm being employed by each manufacturer because of which the patient could not tolerate the Trilogy™ successfully. The most important difference between ResMed and Respironics products is the inspiratory time (Ti time). In ResMed devices, such as VPAP-ST™, Ti is delivered to each breath irrespective of the type of the breath, spontaneous or timed. Each breath has an assured Ti time, known as the Ti minimum. The Ti minimum time set on the patient's VPAP™ device was 1.5 seconds, and thus each breath was guaranteed to have a Ti time of no less than 1.5 seconds. Whereas the Respironics device in ST mode has a set Ti time, the set Ti time only applies to timed breaths. Therefore, in this patient who was predominantly triggering his own breaths according to his download, the patient was not getting the set Ti time; so although it was set in ST mode, it was acting more like S mode. ALS patients, due to the nature of the disease, are not able to prolong the breath and complete the breath early, increasing work of breathing and limiting ventilation. This was happening to our patient when he used the Trilogy™ in ST mode. Therefore, the ideal mode for him

when using the Trilogy™ would have been a pressure control mode (PC) in which he would have gotten a fixed Ti time with every breath and thus more stable ventilation [2]. This is what was done for the patient during the in-clinic titration, and the patient was much more comfortable and able to synchronize his breathing better.

In addition to pressure-cycled ventilation, noninvasive ventilator devices offer the option of volume-cycled modes and newer "hybrid" modalities such as volume-assured pressure support ventilation (e.g., AVAPS™, iVAPS™). AVAPS™ delivers an inspiratory pressure to target a set tidal volume per breath, while iVAPS™ adjusts the positive inspiratory pressure to target a tidal volume during each breath to accomplish a set target "alveolar volume" (i.e., minute ventilation minus estimated dead space ventilation). There is general lack of evidence to guide specific ventilator type or mode selection. A couple of small randomized studies showed AVAPS™ was more effective than bilevel pressure ventilation for delivery of minute ventilation and reducing arterial partial pressure of carbon dioxide ($PaCO_2$) levels, while there was no difference in sleep architecture [3, 4]. The most important thing for choosing ventilator mode should be patient comfort, acceptance, and ability to improve gas exchange and work of breathing. Settings that may be adjusted to ensure comfort and synchrony include trigger sensitivity (controls transition from exhalation to inhalation), inspiratory time, and cycle sensitivity (controls transition from inhalation to exhalation). For example, neuromuscular patients generally have weak respiratory muscles, and therefore a high trigger sensitivity and medium cycle sensitivity setting may help these patients initiate and maintain inspiratory breaths easier. And unlike COPD patients, neuromuscular patients may benefit from greater inspiratory time for alveolar recruitment. For patients with neuromuscular disease and concomitant obstructive sleep apnea, a higher EPAP setting may be required to open the upper airways. To determine the optimal expiratory pressure for obstructive sleep apnea, polysomnography titration or a ventilator with auto-adjusting EPAP features (e.g., Trilogy AVAPS-AE™) may be considered.

The other important fact highlighted in this case is that we performed the titration in the clinic setting instead of overnight polysomnogram. Though the 2011 Noninvasive Positive Pressure Ventilation Titration Task Force of the American Academy of Sleep Medicine recommends initial titration of pressures in a sleep lab to optimize pressure settings in addition to comfort [5], evidence is lacking to demonstrate the superiority of this approach over home initiation or daytime titration. Daytime titration has been shown to reduce mortality in the setting of ALS [6]. This approach reduced the wait times to ventilation commencement and improved survival without a change in the effectiveness of ventilation. Thus, if in-lab polysomnography is not readily available or the lab lacks the appropriate expertise, then initiation of noninvasive ventilation should not be delayed while waiting for a study.

There is a lack of consensus on whether or how to monitor gas exchange during initiation of noninvasive ventilation. End-tidal carbon dioxide measurements are not reliable because of leaks and dilution and often underestimate arterial carbon dioxide levels. Transcutaneous carbon dioxide monitoring systems with oximetry may be helpful if available. There is also no consensus on the best way to monitor ALS

patients on home based noninvasive ventilation. The use of overnight pulse oximetry, arterial blood gas, or transcutaneous carbon dioxide monitoring along with the download from the device could assist in understanding the needs of the patient.

Clinical Pearls

1. Sleep study (i.e., polysomnography) is not required for the diagnosis of hypoventilation. It may be required to assist with titration especially in setting of obstructive sleep apnea to help establish adequate expiratory positive airway pressure.
2. To qualify for noninvasive mechanical ventilation in neuromuscular disease, patients must demonstrate symptoms of hypoventilation and fulfill the following criteria: FVC < 50% predicted, maximal inspiratory pressure < −60 cmH_2O, $PaCO_2$ > 45 mmHg, and oxygen saturation by pulse oximetry <88% for > 5 min during an overnight recording.
3. Selection of the device, mode, and the differences in the algorithms employed by various manufactures need to be kept in mind.
4. Ambulatory titration can be performed with success in these patients.

References

1. Sahni AS, Wolfe L. Respiratory care in neuromuscular diseases. Respir Care. 2018;63:601–8.
2. Selim BJ, Wolfe L, Coleman JM 3rd, Dewan NA. Initiation of noninvasive ventilation for sleep related hypoventilation disorders: advanced modes and devices. Chest. 2018;153:251–65.
3. Ambrogio C, Lowman X, Kuo M, Malo J, Prasad AR, Parthasarathy S. Sleep and noninvasive ventilation in patients with chronic respiratory insufficiency. Intensive Care Med. 2009;35:306–13.
4. Storre JH, Seuthe B, Fiechter R, et al. Average volume-assured pressure support in obesity hypoventilation: a randomized crossover trial. Chest. 2006;130:815–21.
5. Berry RB, Chediak A, Brown LK, et al. Best clinical practices for the sleep center adjustment of noninvasive positive pressure ventilation (NPPV) in stable chronic alveolar hypoventilation syndromes. J Clin Sleep Med. 2010;6:491–509.
6. Sheers N, Berlowitz DJ, Rautela L, Batchelder I, Hopkinson K, Howard ME. Improved survival with an ambulatory model of non-invasive ventilation implementation in motor neuron disease. Amyotroph Lateral Scler Frontotemporal Degener. 2014;15:180–4.

Chapter 13
Alveolar Hypoventilation and Non-invasive Ventilation in COPD

Loutfi S. Aboussouan and Umur Hatipoğlu

Case Presentation

A 61-year-old African-American man presents to the pulmonary clinic for an evaluation 2 weeks following a hospital discharge for a COPD exacerbation. He has had progressively worsening symptoms of shortness of breath over a period of 15 years preceding this clinic presentation. He was a 1 pack-per-day smoker over 40 years and had quit 8 years ago due to worsening shortness of breath. He had also been on oxygen supplementation for the past 7 years. He was previously an iron worker with no history of asbestos or silica exposure but currently disabled. He initially started experiencing exacerbations requiring hospitalization once every other year, but about 3 years ago, he started developing more frequent exacerbations such that in the year preceding this clinic presentation, he had experienced 6 hospitalizations including one with hypercapnic respiratory failure for which invasive mechanical ventilation was required. He had been previously assessed for lung transplantation but he did not wish to pursue that option, citing concerns about the long-term expenses and the burdens on his daughters who lived in different states and on his elderly mother with whom he lived and who was his only caregiver.

Assessment

At the time of this evaluation, he presented in a wheelchair and was back to his baseline. He still had a chronic productive cough and remained very limited in his walking ability even with oxygen supplementation, such that he had trouble with

L. S. Aboussouan (✉) · U. Hatipoğlu
Respiratory Institute, Cleveland Clinic, Cleveland, OH, USA
e-mail: aboussl@ccf.org; hatipou@ccf.org

C. Won (ed.), *Complex Sleep Breathing Disorders*,
https://doi.org/10.1007/978-3-030-57942-5_13

activities of daily living and rarely left his house. He had previously completed a course of pulmonary rehabilitation, which he thought had been helpful but he had not consistently exercised since.

On exam his body mass index was 24 kg/m^2, lungs were hyperresonant to percussion with very diminished air entry, and inspiratory crackles. No wheezes or rhonchi were heard. There was no pedal edema.

An arterial blood gas obtained at that visit (2 weeks after his last hospital admission) showed a pH 7.37, $PaCO_2$ 53 mmHg, PaO_2 64 mmHg, and bicarbonate 29 mEq/L while on 3 L of oxygen by nasal cannula.

An alpha-1 antitrypsin genotype was available in the records and noted to be PI*MM.

A CT scan of the chest showed severe diffuse emphysema with a right upper lobe pulmonary nodule.

Pulmonary function tests were as follows:

	Predicted	Baseline	After bronchodilators	Percent change
FVC (L)	4.56	1.83 (40%)	2.07 (45%)	13
FEV_1 (L)	3.60	0.42 (12%)	0.50 (14%)	18
FEV_1/FVC	78.82	22.91	23.98	5

Abbreviations: *FVC* Forced vital capacity, *FEV_1* forced expiratory volume in the first second

On a 6-minute walk test he was able to walk 598 feet (180 m) and maintained his oxygen saturation at 93% while on 6 L of supplemental oxygen.

Management

He was maintained on an optimal inhaler regimen consisting of dry powder inhaler formulations of fluticasone/salmeterol 500 mcg/50 mcg 1 puff twice daily and tiotropium 18 mcg 1 puff daily. Because of the chronic bronchitis component of his presentation, he was started on roflumilast 500 mcg orally once daily. He continued nebulized albuterol, which he required 4 times daily because of persistent symptoms of shortness of breath, and oxygen 4 L at rest and 5 L with exertion. Pulmonary rehabilitation was initiated. Non-invasive positive pressure ventilation was prescribed at an initial pressure of IPAP 12 cmH_2O and EPAP 5 cmH_2O without a back-up rate.

Outcome

He did not adapt immediately to the intervention, but by the time of his clinic follow-up 3 months later, he was using non-invasive ventilation regularly for about 8 h per night. Over the subsequent year, he progressed to using the device in the daytime as well while awake for relief of symptoms, for a total of 11 h per day. He felt

significantly improved. He was particularly grateful for the sense of control non-invasive ventilation gave him over his disease, and for a significant reduction in hospitalizations. He also felt that roflumilast effectively treated his bronchitis symptoms, but he had to stop tiotropium due to urinary retention. Although the exacerbation rate improved, his pulmonary rehabilitation program was interrupted by a hospitalization for an exacerbation in the year following initiation of non-invasive ventilation. A follow-up computed tomography of the lungs scan showed resolution of the right upper lobe nodule considered in retrospect to have been inflammatory in nature. He continued to worsen in his activity tolerance such that 2 years after initiation of non-invasive ventilation his 6-minute walking distance had decreased to 360 feet (110 m) while on 6 L of oxygen supplementation. He was managed mostly at home and was admitted to hospice 5 years after initiation of non-invasive ventilation where he expired 3 months later.

Discussion

Several mechanisms that serve to preserve carbon dioxide homeostasis are altered in patients with severe COPD. Work of breathing is increased due to elevated elastic load, a consequence of static and dynamic hyperinflation and elevated resistive load due to airflow limitation. Furthermore, respiratory muscle force generation is reduced in COPD owing to both shortened inspiratory muscle fibers consequent to hyperinflation and reduced muscle strength [1, 2]. Faced with mechanical constraints and diminished pump capacity, the respiratory controller adopts lower tidal volumes and faster respiratory rates [3], to avoid respiratory muscle fatigue [4]. The adoption of lower tidal volumes further worsens dead space ventilation, already problematic in COPD due to alveolar destruction, predisposing to carbon dioxide retention. Although mechanisms are not fully elucidated, it has been hypothesized that under these dire circumstances, central controller selects “submissive hypercapnia” to conserve energy and prevent task failure [5]. In support of this theory, the minute ventilation-carbon dioxide slope is significantly reduced among patients with severe COPD when compared to patients with congestive heart failure with similar exercise capacity [6]. Further, normal subjects reduce diaphragmatic recruitment when subjected to excessive inspiratory loads to avoid muscle fatigue, suggesting a similar load compensation strategy exists in health [7]. Non-invasive ventilation unloads respiratory muscles and ameliorates mechanical constraints by offsetting elastic threshold load and dynamic airway collapse and thus offers potential reversal of the aforementioned adverse circumstances and consequent respiratory controller adaptation.

Non-invasive ventilation has long been acknowledged as a standard of care for the in-hospital management of acute exacerbation of COPD associated with hypercapnic respiratory failure, with strong evidence stemming from several randomized trials [8]. In contrast, the experience with non-invasive ventilation in the home

setting as a chronic intervention for individuals with stable COPD remains limited though more current evidence supports its use in select individuals.

The adoption of non-invasive ventilation in the home setting for stable COPD has been slow with significant doubts and concerns that it may be ineffective, poorly tolerated [9, 10], may worsen quality of life [11], and reduce sleep efficiency [10, 12]. Hyperinflation of the lungs may be a factor that reduces adherence to non-invasive ventilation in patients with the COPD sleep apnea overlap [13]. Subsequent studies have helped define a subset of COPD patients as well as device settings associated with improved quality or life, adherence, exacerbation frequency, and survival. The current accepted approach is to use high pressure-support settings aimed at reducing chronic daytime hypercapnia in severe but stable COPD.

The impetus to use high pressures stems from randomized trials which compared non-invasive ventilation at high-intensity (mean inspiratory pressure of 29 cmH_2O, mean expiratory pressure just under 5 cmH_2O with back-up rate 18 breaths/min) to low-intensity (mean inspiratory pressure 15 cmH_2O, mean expiratory pressure 4 cmH_2O with back-up respiratory rate 8). The high intensity arm increased FEV_1, reduced daytime and nocturnal $PaCO_2$, increased adherence by 3.6 h/day, and improved exercise-related dyspnea and health-related quality of life [14, 15]. Although these studies also favored a high back-up rate on the device to maximally reduce the $PaCO_2$, there may be no particular benefit of a high back-up rate in improving adherence [16]. In a randomized controlled trial of low-intensity noninvasive positive-pressure ventilation with oxygen compared with oxygen alone in hypercapnic COPD, there was a potential survival benefit in the adjusted analysis for non-invasive ventilation, and good adherence, but at the expense of a significant deterioration in general and mental health, as well as worsening in mood [11].

There have been several randomized trials of non-invasive ventilation in stable COPD [10–12, 17–24], including some that looked at hard outcomes of survival and readmission rate (Table 13.1). The selection of patients with hypercapnia in a stable state appears to be an important determinant of a favorable outcome. For instance, in one randomized study, high-intensity non-invasive ventilation was initiated for persistent hypercapnia prior to discharge from hospital for an episode of acute respiratory failure requiring ventilation [23]. That study which targeted patients in an acute rather than chronic hypercapnic state failed to show a favorable impact of the intervention on readmission, mortality, exacerbations, lung function, or quality of life in the first year following the index admission [23]. In sharp contrast, significant survival advantages and/or delay in hospitalization were noted when the intervention targeted COPD patients who had hypercapnia with a $PaCO_2 > 52$ mmHg in a stable state including several weeks after a hospitalization for an exacerbation [21, 22].

Our patient had severe group D COPD based on the GOLD classification [25], with severely limited exercise tolerance and frequent exacerbations requiring hospitalization. The exacerbations persisted despite an effective inhaler and medication regimen. Even though the pressures selected in our patient were low relative to

current recommended settings, he felt a significant benefit after a short period of adaptation, became adherent to the intervention within 3 months of its initiation, and there was a significant reduction in exacerbations and hospitalizations. Despite concerns from some studies that quality of life may be compromised with the use of non-invasive ventilation, our patient felt that the device was quite helpful with his specific comment that it provided him with a sense of control over his disease. This is consistent with studies showing an improvement in mastery score on the chronic respiratory disease questionnaire with the device [17]. His device did not include a back-up rate but some studies attribute the improvement to the pressure support rather than the back-up rate [16], and a survival benefit may occur even in the absence of a back-up rate [11].

In conclusion, chronic nocturnal non-invasive ventilation may be effective in appropriately selected COPD patient with hypercapnia either in the stable state or which persists for 2 or more weeks after requiring acute non-invasive ventilation for an exacerbation [26]. Although the precise cutoff is different between studies (Table 13.1), a $PaCO_2$ of >52 mmHg is one of the criteria adopted by the Centers of Medicare and Medicaid Services (CMS) to qualify for non-invasive ventilation in the setting of COPD (the other criteria being documentation of nocturnal desaturation <88% for >5 min on prescribed FiO_2, and exclusion of sleep apnea) [27]. This cutoff concords with that of other randomized trials [21, 22]. With selection of appropriate patients and with high-intensity settings, the benefits of non-invasive ventilation include improvement in survival [11, 21], readmissions [22], exacerbation frequency [22], health-related quality of life [21, 22, 24], and FEV_1 [21, 24]. More studies may be needed to clarify patient and settings selection especially as far as potential confounding by sleep apnea which have not been adequately addressed

Table 13.1 Randomized studies of non-invasive ventilation in stable COPD with survival and readmission outcomes

						Device settings		Deaths at 1year (%)		Readmissions at 1year (%)	
Reference	N	Age (yrs)	FEV_1 (%)	$PaCO_2$ (mmHg)	Selection	IPAP/EPAP (cmH_2O), Rate	Adherence (h/night)	T	C	T	C
Casanova [18]	52	66	30	52	Stable clinical FEV_1< 45%	12/4,--	5.9	22	22	19*	18*
Clini [19]	56	65	29	55	Stable $PaCO_2$> 50 mmHg	14/2,8	9	18	17		
McEvoy [11]	144	68	24	54	Stable $PaCO_2$> 46 mmHg	13/5,--	4.5	17†	22†		
Struik [23]	201	64	26	58	$PaCO_2$> 45 mmHg while off support > 48h after hospital admission	19/5, 15	6.3	30	29	56	57
Kohnlein [21]	195	63	27	58	Stable state with $PaCO_2$≥52 mmHg	22/15, 16	5.9	12	33		
Murphy [22]	116	67	23	59	$PaCO_2$> 53 mmHg and low PaO_2> 2 weeks after exacerbation with ventilation	24/6, 14	7.6	28	32	ARR 17% for readmission or deathat 1year.	

* estimated from figure provided †Data obtainedfrom editorial by Elliott [30]Adjusted survival analysis hazard ratio 0.63 (95% CI 0.40 to 0.99, p = 0.045)
Shaded areas represent significant differences
Abbreviations: ARR: absolute risk reduction, FEV_1: forced expiratory volume in 1 second, IPAP/EPAP: inspiratory/expiratory positive airway pressure. T/C: treatment/control arms

in the studies reported [28], the role of a back-up rate on the devices [16], and whether higher EPAP may be helpful to counteract any threshold load imposed by intrinsic PEEP in these patients [29]. Finally, when considering high-intensity non-invasive ventilation, there are theoretical concerns about over-ventilation and arrhythmogenesis due to induced alkalemia. Therefore, CO_2 levels (either via transcutaneous or end-tidal CO_2 monitoring during sleep, or post-sleep arterial blood gas) should be closely monitored initially while determining IPAP/pressure support settings.

Clinical Pearls/Pitfalls

- Despite initial concerns, home non-invasive ventilation can be effective in selected patients with COPD.
- Individuals expected to benefit from the use of non-invasive ventilation include those with chronic hypercapnia ($PaCO_2 > 52$ mmHg) while in a stable state including more than 2 weeks after hospitalization for an episode of acute respiratory failure.
- In addition to patient selection, the choice of device settings is important with studies showing a potential benefit of home non-invasive ventilation generally with settings aimed to correct the hypercapnia (e.g., IPAP 19–24 cmH_2O, and EPAP 4–6 cmH_2O).
- Although high back-up rates (14–18 breaths/min) can also be used, there may be no particular advantage to a back-up rate to improve adherence.
- Expected benefits include a reduced risk of readmission, improved survival, health-related quality of life, and improved device tolerance.
- Close monitoring of CO_2 levels (either via transcutaneous or end-tidal CO_2, or arterial blood gases) should be undertaken when initially determining non-invasive ventilation settings to avoid acute alkalemia and resultant arrhythmias.

References

1. Newell SZ, McKenzie DK, Gandevia SC. Inspiratory and skeletal muscle strength and endurance and diaphragmatic activation in patients with chronic airflow limitation. Thorax. 1989;44(11):903–12.
2. Polkey MI, Kyroussis D, Hamnegard CH, Mills GH, Green M, Moxham J. Diaphragm strength in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1996;154(5):1310–7. https://doi.org/10.1164/ajrccm.154.5.8912741.
3. Sorli J, Grassino A, Lorange G, Milic-Emili J. Control of breathing in patients with chronic obstructive lung disease. Clin Sci Mol Med. 1978;54(3):295–304.
4. Bellemare F, Grassino A. Effect of pressure and timing of contraction on human diaphragm fatigue. J Appl Physiol Respir Environ Exerc Physiol. 1982;53(5):1190–5. https://doi.org/10.1152/jappl.1982.53.5.1190.

5. Poon CS, Tin C, Song G. Submissive hypercapnia: why COPD patients are more prone to CO_2 retention than heart failure patients. Respir Physiol Neurobiol. 2015;216:86–93. https://doi.org/10.1016/j.resp.2015.03.001.
6. Teopompi E, Tzani P, Aiello M, Ramponi S, Visca D, Gioia MR, et al. Ventilatory response to carbon dioxide output in subjects with congestive heart failure and in patients with COPD with comparable exercise capacity. Respir Care. 2014;59(7):1034–41. https://doi.org/10.4187/respcare.02629.
7. Laghi F, Shaikh HS, Morales D, Sinderby C, Jubran A, Tobin MJ. Diaphragmatic neuromechanical coupling and mechanisms of hypercapnia during inspiratory loading. Respir Physiol Neurobiol. 2014;198:32–41. https://doi.org/10.1016/j.resp.2014.03.004.
8. Osadnik CR, Tee VS, Carson-Chahhoud KV, Picot J, Wedzicha JA, Smith BJ. Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2017;7:CD004104. https://doi.org/10.1002/14651858.CD004104.pub4.
9. Hill NS. Noninvasive ventilation has been shown to be ineffective in stable COPD. Am J Respir Crit Care Med. 2000;161(3 Pt 1):689–90; discussion 91. https://doi.org/10.1164/ajrccm.161.3.16135b.
10. Strumpf DA, Millman RP, Carlisle CC, Grattan LM, Ryan SM, Erickson AD, et al. Nocturnal positive-pressure ventilation via nasal mask in patients with severe chronic obstructive pulmonary disease. Am Rev Respir Dis. 1991;144(6):1234–9. https://doi.org/10.1164/ajrccm/144.6.1234.
11. McEvoy RD, Pierce RJ, Hillman D, Esterman A, Ellis EE, Catcheside PG, et al. Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial. Thorax. 2009;64(7):561–6. https://doi.org/10.1136/thx.2008.108274.
12. Lin CC. Comparison between nocturnal nasal positive pressure ventilation combined with oxygen therapy and oxygen monotherapy in patients with severe COPD. Am J Respir Crit Care Med. 1996;154(2 Pt 1):353–8. https://doi.org/10.1164/ajrccm.154.2.8756806.
13. Theerakittikul T, Hatipoglu U, Aboussouan LS. Hyperinflation on chest radiograph as a marker of low adherence to positive airway pressure therapy in the overlap syndrome. Respir Care. 2014;59(8):1267–74. https://doi.org/10.4187/respcare.03011.
14. Dreher M, Storre JH, Schmoor C, Windisch W. High-intensity versus low-intensity non-invasive ventilation in patients with stable hypercapnic COPD: a randomised crossover trial. Thorax. 2010;65(4):303–8. https://doi.org/10.1136/thx.2009.124263.
15. Windisch W, Haenel M, Storre JH, Dreher M. High-intensity non-invasive positive pressure ventilation for stable hypercapnic COPD. Int J Med Sci. 2009;6(2):72–6.
16. Murphy PB, Brignall K, Moxham J, Polkey MI, Davidson AC, Hart N. High pressure versus high intensity noninvasive ventilation in stable hypercapnic chronic obstructive pulmonary disease: a randomized crossover trial. Int J Chron Obstruct Pulmon Dis. 2012;7:811–8. https://doi.org/10.2147/COPD.S36151.
17. Bhatt SP, Peterson MW, Wilson JS, Durairaj L. Noninvasive positive pressure ventilation in subjects with stable COPD: a randomized trial. Int J Chron Obstruct Pulmon Dis. 2013;8:581–9. https://doi.org/10.2147/COPD.S53619.
18. Casanova C, Celli BR, Tost L, Soriano E, Abreu J, Velasco V, et al. Long-term controlled trial of nocturnal nasal positive pressure ventilation in patients with severe COPD. Chest. 2000;118(6):1582–90.
19. Clini E, Sturani C, Rossi A, Viaggi S, Corrado A, Donner CF, et al. The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. Eur Respir J. 2002;20(3):529–38.
20. Garrod R, Mikelsons C, Paul EA, Wedzicha JA. Randomized controlled trial of domiciliary noninvasive positive pressure ventilation and physical training in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2000;162(4 Pt 1):1335–41. https://doi.org/10.1164/ajrccm.162.4.9912029.

21. Kohnlein T, Windisch W, Kohler D, Drabik A, Geiseler J, Hartl S, et al. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. Lancet Respir Med. 2014;2(9):698–705. https://doi.org/10.1016/S2213-2600(14)70153-5.
22. Murphy PB, Rehal S, Arbane G, Bourke S, Calverley PMA, Crook AM, et al. Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: a randomized clinical trial. JAMA. 2017;317(21):2177–86. https://doi.org/10.1001/jama.2017.4451.
23. Struik FM, Sprooten RT, Kerstjens HA, Bladder G, Zijnen M, Asin J, et al. Nocturnal noninvasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study. Thorax. 2014;69(9):826–34. https://doi.org/10.1136/thoraxjnl-2014-205126.
24. Duiverman ML, Wempe JB, Bladder G, Vonk JM, Zijlstra JG, Kerstjens HA, et al. Two-year home-based nocturnal noninvasive ventilation added to rehabilitation in chronic obstructive pulmonary disease patients: a randomized controlled trial. Respir Res. 2011;12:112. https://doi.org/10.1186/1465-9921-12-112.
25. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. Am J Respir Crit Care Med. 2017;195(5):557–82. https://doi.org/10.1164/rccm.201701-0218PP.
26. Storre JH, Callegari J, Magnet FS, Schwarz SB, Duiverman ML, Wijkstra PJ, et al. Home noninvasive ventilatory support for patients with chronic obstructive pulmonary disease: patient selection and perspectives. Int J Chron Obstruct Pulmon Dis. 2018;13:753–60. https://doi.org/10.2147/COPD.S154718.
27. Local Coverage Determination (LCD): Respiratory Assist Devices (L33800) for DME MAC Jurisdictions A, B, C, and D. Available at https://www.cms.gov/medicare-coverage-database/
28. Hill NS, Ugurlu AO. Home noninvasive ventilation to reduce readmissions for chronic obstructive pulmonary disease. JAMA. 2017;317(21):2167–9. https://doi.org/10.1001/jama.2017.5226.
29. MacIntyre NR, Cheng KC, McConnell R. Applied PEEP during pressure support reduces the inspiratory threshold load of intrinsic PEEP. Chest. 1997;111(1):188–93.
30. Elliott M. Domiciliary NIV for COPD: where are we now? Lancet Respir Med. 2014;2(9):672–3. https://doi.org/10.1016/s2213-2600(14)70159-6.

Chapter 14
Hypoventilation Associated with Scoliosis

Sritika Thapa and Janet Hilbert

Abbreviations

ABG	Arterial blood gas
AVAPS	Average volume assured pressure support
BMI	Body mass index
BPAP	Bilevel positive airway pressure
BPAP-S	Bilevel positive airway pressure spontaneous mode
BPAP-ST	Bilevel positive airway pressure spontaneous-timed mode
EPAP	Expiratory positive airway pressure
ERV	Expiratory reserve volume
FRC	Functional residual capacity
HMV	Home mechanical ventilator
IPAP	Inspiratory positive airway pressure
NIPPV	Noninvasive positive pressure ventilation
NMD	Neuromuscular diseases
NREM	Non-rapid eye moment
PCV	Pressure control ventilation
PFT	Pulmonary function test
PS	Pressure support
PSG	Polysomnography
RAD	Respiratory assist device

S. Thapa (✉) · J. Hilbert
Pulmonary, Critical Care and Sleep Medicine, Yale University, New Haven, CT, USA
e-mail: sritika.thapa@yale.edu

C. Won (ed.), *Complex Sleep Breathing Disorders*,
https://doi.org/10.1007/978-3-030-57942-5_14

REM	Rapid eye movement
$TcCO_2$	Transcutaneous carbon dioxide
TLC	Total lung capacity
TV	Tidal volume
V/Q	Mismatch ventilation perfusion mismatch
VAPS	Volume assured pressure support
VC	Vital capacity

Case

AB is a 51-year-old woman with a history of prior tracheostomy for unspecified lung surgery as an infant and scoliosis (status post placement of Harrington rods at the age of 14) who was referred to the sleep clinic for consideration of noninvasive positive pressure ventilation (NIPPV) following recent hospitalization for acute on chronic hypercapnic respiratory failure. Prior to that hospitalization, she reported a 3-week history of dyspnea on exertion, orthopnea, and lower extremity edema, which then worsened prompting admission. She had minimal cough but denied fever, chest pain, palpitations, and dyspnea on bending forward. During her hospitalization, no acute etiology was found. She was treated with diuretics, bronchodilators, and antibiotics and discharged home.

During her sleep clinic visit 3 weeks after discharge, she reported significantly improved dyspnea overall, but still mild dyspnea on exertion. Sleep history was unremarkable, with only occasional snoring without witnessed apnea, gasping awakenings, or symptoms of non-respiratory sleep disorders. Epworth sleepiness score was 2.

Other prior medical history was only positive for sickle cell trait. Medications included Vitamin B12, multivitamin, inhaled ipratropium-albuterol as needed, and levonorgestrel. She endorsed an allergy to penicillin. She was a never-smoker, non-drinker, with no prior illicit drug use. She worked as a telephone operator.

Physical exam revealed blood pressure 132/90 mmHg, heart rate 102 beats per minute and oxygen saturation by pulse oximetry (SpO_2) of 96%. Her body mass index (BMI) was 25 kg/m^2. She was in no acute distress on general exam. Examination of the head and neck revealed a normal nasal septum, no turbinate hypertrophy, Mallampati Score 3, no scalloping of tongue, grade 1 tonsils. Her neck revealed healed surgical scar and no lymphadenopathy. Her lungs were clear without wheezes, rhonchi, or rales. Heart was regular without murmur. No peripheral edema was present. Back was asymmetric with a longitudinal scar. The rest of her exam was normal.

Hospital data were reviewed. Initial arterial blood gas (ABG), performed on oxygen, showed pH 7.28, $PaCO_2$ 96 mmHg, PaO_2 121 mmHg, which improved to pH 7.40, $PaCO_2$ 60 mmHg, PaO_2 69 mmHg by discharge 8 days later. Chest X-ray showed chest wall deformity, scoliosis with prominent dextrocurvature of the thoracolumbar spine with rods in place and left lower lobe atelectasis (Fig. 14.1). Chest

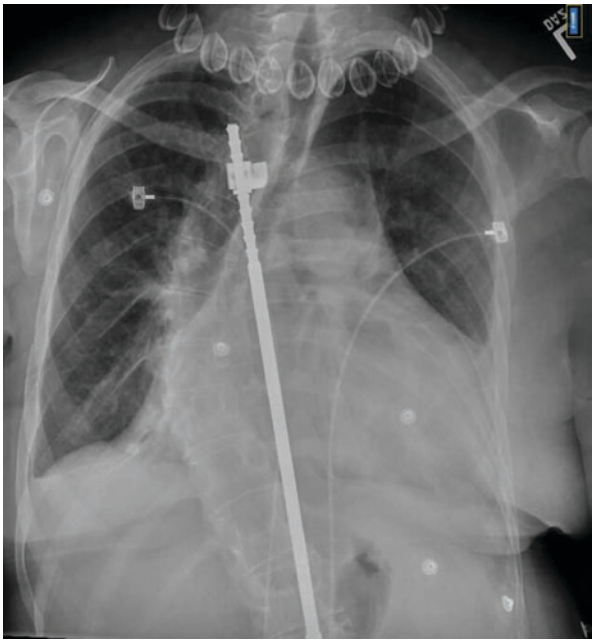


Fig. 14.1 Chest X-ray PA view showing chest wall deformity-scoliosis with prominent dextrocurvature of the thoracolumbar spine with Harrington rods in place and left lower lobe atelectasis

CT showed no pulmonary embolus, enlarged right-sided cardiac chamber with signs of elevated right heart pressure, small right pleural and pericardial effusions, and near-complete atelectasis of the right lower lobe. Chest ultrasound showed diaphragmatic motion bilaterally during inspiratory effort with decreased motion of the left hemidiaphragm compared to the right. Echocardiogram showed normal left ventricular ejection fraction but flattened septum consistent with right ventricular pressure and volume overload, moderately increased right ventricular cavity size with reduced systolic function and increased right ventricular systolic pressure of 75 mmHg. Right heart catheterization after diuresis and prior to discharge showed right atrial pressure 3 mmHg, right ventricular pressure 55/4 mmHg, pulmonary artery pressure 35/15 mmHg with mean of 22 mmHg, pulmonary capillary wedge pressure of 8 mmHg, cardiac output 4.23 L/min, and cardiac index 2.40 L/min/cm^2.

Pulmonary function testing (PFT) done 2 weeks after discharge and 1 week prior to sleep clinic visit showed severe restriction without obstruction with moderate reduction in diffusion capacity. Forced expiratory volume in 1 s (FEV1) 0.75 L (29%), forced vital capacity (FVC) 1.07 L (31%), FEV1/FVC ratio 71%, total lung capacity (TLC) 1.89 L (36%), and diffusion capacity of the lungs for carbon monoxide (DLCO) 8.55 L (42%). Nocturnal oximetry on room air done 3 weeks after discharge and 1 day prior to sleep clinic visit revealed sustained hypoxemia at baseline, with three discrete periods of desaturation suggestive of rapid eye movement (REM) worsening, with overall mean SpO_2 of 82%, nadir SpO_2 of 53%, and 335.3 min with $SpO_2 \leq 88\%$ (Fig. 14.2).

Based on the clinical history and persistent sustained sleep-related hypoxemia, criteria to initiate NIPPV were met. ABG performed on room air just prior to

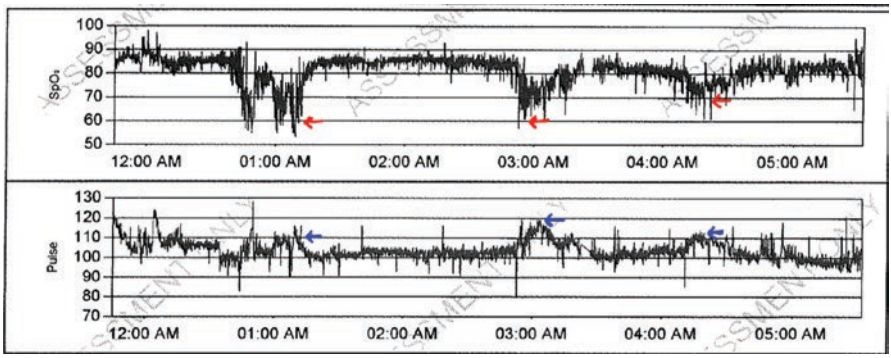


Fig. 14.2 Nocturnal pulse oximetry shows sustained hypoxemia and three discrete periods of significant worsening (red arrows, top panel) which is suggestive of REM worsening. These worsening also correlate with pulse variability (blue arrows, bottom panel)

therapeutic polysomnography (PSG) showed further improvement in diurnal gas exchange (pH 7.41, $PaCO_2$ 43, PaO_2 65). PSG on average volume assured pressure support (AVAPS) with target tidal volume of 8 cc/kg was performed. Sleep architecture revealed scattered awakenings with two REM periods (Fig. 14.3). The patient slept entirely nonsupine. There was no significant obstructive sleep apnea (apnea-hypopnea index of 4/h by American Academy of Sleep Medicine criteria). Overall oxygenation was improved compared with baseline nocturnal oximetry (although not optimal) with persistent sleep-related hypoventilation characterized by decreased SpO_2 and increased transcutaneous carbon dioxide ($TcCO_2$), especially in REM sleep (Fig. 14.3). Mean SpO_2 was 91% with nadir SpO_2 of 76% and 17% of time with $SpO_2 \leq 88$, despite adjustment of target tidal volume and added oxygen. $TcCO_2$ was 63–64 mmHg in non-rapid eye moment (NREM) sleep and 66–67 mmHg in REM sleep. At the conclusion of the test, the patient reported that she felt much better on awakening in the morning compared with home. AVAPS was ordered for home use, with plan for close follow-up including assessment of symptoms, objective data from device (i.e., adherence, efficacy, respiratory parameters, mask leak), home oximetry on AVAPS, daytime ABG, and eventual repeat therapeutic PSG.

Discussion

Introduction

Chronic alveolar hypoventilation may be secondary to chronic obstructive pulmonary disease, obesity hypoventilation syndrome, restrictive ventilatory disorders including thoracic wall abnormalities and neuromuscular diseases (NMD), or centrally acting mechanisms (e.g., opioids) [1]. Thoracic wall disorders include

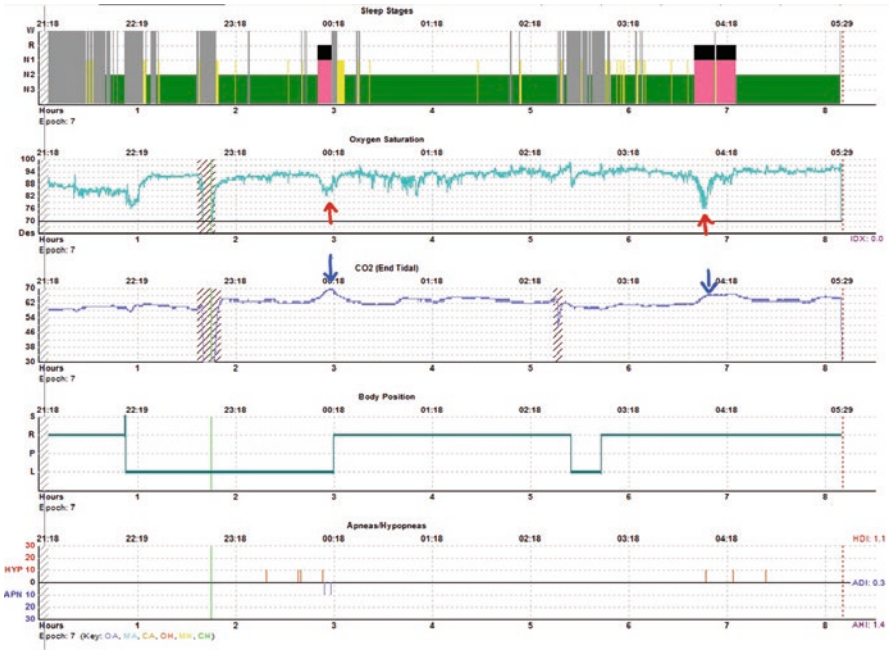


Fig. 14.3 Polysomnography hypnogram demonstrating worsening of hypoxemia (single arrows) and worsening of hypercapnia (double arrows) in REM stage (circled)

diseases and deformities of the rib cage (thoracic spine, ribs and sternum, muscles of respirations (diaphragm, intercostal muscles), and abdomen [2]. These disorders lead to restrictive defects due to reduced chest wall compliance leading to increased work of breathing by placing an elastic load on the respiratory muscles and eventually some reduction in lung compliance from atelectasis. Severe chest wall deformity leads to reduced expiratory reserve volume (ERV) that in turn leads to reduced functional residual capacity (FRC), vital capacity (VC), and total lung capacity.

Epidemiology

Scoliosis is a spinal disease caused by excessive spinal curvature in coronal plane with an angle of curvature more than 10° of Cobb angle. Cobb angle is measured by first identifying the apex vertebra, which is at the deepest part of the scoliosis curve, and then 2 vertebras, one above and one below the apex whose endplates are most tilted toward each other. Lines are drawn along the endplates of these two vertebras and the angle between the intersected lines is measured which gives the Cobb angle. Kyphosis (curvature in the sagittal plane) is commonly associated with scoliosis.

Kyphoscoliosis affects 4% of the population. Prevalence of severe kyphoscoliosis with Cobb angle >100° impairing chest mechanics or >120° resulting in

respiratory failure is 1 in 10,000 [2]. These patients have reduction in VC which may be reduced to 30% of predicted or less in individuals with Cobb angle >90% [3].

Females are affected more than males in a 3–4:1 ratio. Scoliosis is idiopathic in more than 80% of patients. In the remaining, it is secondary to neuromuscular disease, congenital defects, tumors, or trauma.

Clinical Presentation

Patients with restrictive thoracic disorders may have disrupted nighttime sleep; excessive daytime sleepiness; nocturnal, or morning headache (likely from the increased $PaCO_2$); and dyspnea [4]. Dyspnea may become more apparent with supine positioning or during exertion. There may be fatigue and decreased exercise capacity or there may be minor or no complaints [5].

The clinical course and prognosis depend on the cause and progression of scoliosis, pattern of deformity, and age of onset [2]. Cobb angles of 50^0 or less have minimal effects on respiratory system compliance but those greater than 100^0 may have compliance decreased similar to patients with acute respiratory distress syndrome leading to respiratory failure [3]. Patients with angle less than 70° may be asymptomatic, those in between 70° and 100° may become symptomatic in middle age (which may have been the case in our patient) and those with 90° or greater have restrictive defects with exertional dyspnea and exercise intolerance as the early manifestations [2]. However, the degree of nocturnal desaturation may not correlate with the angle of spinal deformity [3]. Onset of kyphoscoliosis before the age of 8 years can lead to rapid decline in pulmonary function, pulmonary hypertension, and respiratory failure while the idiopathic kyphoscoliosis with onset around puberty may have a good prognosis [6].

Polysomnographic Findings

The classic sleep-disordered breathing pattern in restrictive thoracic disorders and neuromuscular disease is hypoventilation, which occurs initially in REM sleep, then progressing into NREM sleep though still being worse in REM, and, finally, occurring during wakefulness [7]. Small case series have shown worsening sleep-disordered breathing in REM in patients with scoliosis [8–10]. In one study, either no apnea or prolonged central apneas in REM were seen [8], while in another, both central and obstructive respiratory disturbances were reported [9]. In yet another study, significant sleep apnea was not identified [10]. Our patient demonstrated the pattern of hypoventilation during sleep out of proportion to wakefulness with worsening in REM compared with NREM sleep. Decreased REM and stage N3 sleep and increased N1 and N2 sleep have been reported [9].

Pathophysiology

Initially there is reduced chest wall compliance in scoliosis, which changes the resting position of the chest wall and reduces the FRC. Gradually, lung compliance also decreases due to atelectasis and air trapping from breathing at low lung volumes. There is also inspiratory muscle weakness, mainly in the diaphragm due to the deformity of the rib cage that changes the length and orientation of the respiratory muscles [11]. Chest wall compliance also decreases with age, and there is a worsening of respiratory mechanics with age without a worsening of spinal deformity.

Due to limitation in lung expansion, tidal volume (TV) falls (which initially is compensated by increased respiratory rate) leading to hypoventilation. Because of shallow breathing, there is increased dead space ventilation which causes alveolar hypoventilation [12]. There may also be impaired inspiratory muscle function independent of primary neurological disease that further contributes to the hypoventilation [13]. This respiratory muscle weakness is further worsened by hypercapnia and hypoxia leading to respiratory failure.

There is only mild hypoxemia from ventilation/perfusion mismatch (V/Q mismatch) without hypercapnia in mild to moderate scoliosis initially. This mismatch is due to asymmetry between the right and left lungs from scoliosis; the lungs on the convex side are better ventilated than on the concave side [2]. However, as the disease progresses, V/Q mismatch worsens, further progressing hypoxemia. V/Q mismatch is the primary mechanism for hypoxemia in scoliosis [12, 14]. Shallow tidal breaths from decreased respiratory compliance and breathing at low lung volumes (due to decrease in FRC) can lead to atelectasis, which may worsen hypoxemia by pulmonary shunting [3].

Additionally, in the supine position, the diaphragm ascends up into the chest, and the lungs are compressed which leads to reduction of ERV and FRC (in scoliosis FRC is already reduced and hence there is further reduction). Due to this, dependent airways close within the range of tidal breathing and there is regional alveolar V/Q mismatch worsening hypoxemia [15]. Positional hypoxemia is further worsened during sleep and particularly during REM sleep. The fall in SpO_2 in sleep has been shown to be directly related to the rise in $TcCO_2$, suggesting hypoventilation as an important mechanism for sleep-related hypoxemia [10].

Compared with NREM sleep, there is further worsening of desaturation in REM sleep. Patients with chest wall abnormalities depend mostly on accessory respiratory muscles for ventilation. However, during REM sleep, accessory muscles of respiration are inhibited. This causes compensatory increase in diaphragmatic effort, which leads to paradoxical chest wall motion and instability of thoracic cage. This further contributes to atelectasis, abnormal distribution of inspired air, and hypoventilation causing ventilation and perfusion mismatch [4].

These patients may also have decreased drive to breathe, which further worsens hypoventilation both during sleep and wakefulness. This causes chronic hypercapnia and hypoxia, which leads to pulmonary arterial vasoconstriction. Eventually this

leads to pulmonary hypertension and cor pulmonale [4], as was seen in our patient during her hospitalization. This abnormality in breathing patterns and blunted hypoxic drive leads to severe hypoxemia in addition to their already low oxygen reserve from reduced FRC [8].

Hence, nocturnal hypoxemia can be worsened in kyphoscoliotic patients due to various factors including gas exchange abnormalities, inspiratory muscle weakness, abnormal breathing pattern, blunted hypoxic drives, and some predispositions toward apnea with further worsening in REM sleep stages. In a small case series, degree of thoracic deformity, pulmonary function test, arterial $PaCO_2$, or chemical drives were not predictive of sleep-disordered breathing [8].

Treatment

NIPPV is effective in treating hypoventilation in restrictive thoracic disorders [16]. Long-term NIPPV therapy improves respiratory muscle function by reducing the work of breathing and improves daytime blood gas levels by resetting the CO_2 sensitivity. It thus may be used to treat hypercapnia and hypoxemia and improve hypoventilation-based clinical symptoms [4, 11, 16]. The positive end expiratory pressure may improve oxygenation through alveolar recruitment especially in atelectatic lung along with improvement of obstructive events.

Per a 1999 multi-society consensus conference, NIPPV is recommended in patients with restrictive thoracic disorders who meet the following criteria: [1] symptoms of hypoventilation (e.g., morning headache, dyspnea, fatigue) and any one of the following physiologic criteria [2] (a) $PaCO_2 \geq 45$ mmHg; (b) nocturnal oximetry with saturation $\leq 88\%$ for 5 consecutive minutes; and (c) FVC (forced vital capacity) <50% predicted [16]. On a practical note, in the United States, a respiratory assist device (RAD) capable of delivering bilevel positive airway pressure therapy with or without a backup rate is a covered medical expense in restrictive thoracic disorders if the following criteria are met: (1) severe thoracic cage abnormality documented and (2) chronic obstructive lung disease does not contribute significantly and (3) any ONE of (a) $PaCO_2 \geq 45$ mmHg while awake and on prescribed FIO_2, (b) nocturnal oximetry with $SpO_2 \leq 88\%$ for ≥ 5 min (not necessarily consecutive) on prescribed FIO_2 (minimum recording time 2 h) [7]. A home mechanical ventilator (HMV) capable of delivering more advanced modes of NIPPV may be covered for more severe or recurrent respiratory failure. Diagnostic polysomnography with CO_2 monitoring may be helpful in further characterizing sleep-disordered breathing [7] or predicting need for future NIPPV [17], but is not required by current clinical practice guidelines or third-party payers. Thus, diagnostic workup should include, at minimum, careful history, assessment of pulmonary function, ABG, and nocturnal oximetry.

Once a decision is made to initiate NIPPV, initial mode, device, interface, and settings need to be selected and titrated for optimal results. There are several

recent, practical reviews for guidance [1, 18, 19], but few studies have been performed in thoracic cage disorders. Technology is rapidly evolving, and NIPPV preferences vary with institution. Most common modes are bilevel positive airway pressure (BPAP) modes, either in spontaneous mode (BPAP-S) or in spontaneous-timed mode (BPAP-ST), with more recent emergence of "hybrid" modes that use additional software to help assure an average tidal volume (VAPS) or average minute ventilation. The expiratory positive airway pressure (EPAP) provides pressure to maintain upper airway patency, while the difference between the inspiratory positive airway pressure (IPAP) and EPAP is the level of pressure support (PS). Assuming adequate EPAP and airway patency, PS determines tidal volume, which varies breath-by-breath depending on inspiratory time, lung compliance, and airways resistance. With VAPS technology, an average tidal volume or average minute ventilation is set, allowing PS to vary as needed to reach these average targets. A few devices with VAPS capability have introduced an auto-EPAP algorithm in which the EPAP will adjust accordingly to assure upper airway patency that is needed to deliver the PS to the lower airway [1]. Pressure control ventilation (PCV) is also available on some devices and is used selectively.

In general, in the absence of obstructive sleep apnea, EPAP is set relatively low, and PS is set to achieve adequate ventilation while maximizing comfort and minimizing asynchrony. Initial settings may be empiric with outcomes assessed clinically or titration PSG may be performed. The 2010 American Academy of Sleep Medicine Clinical Practice Guideline recommends PSG for titration of NIPPV in chronic alveolar hypoventilation due to restrictive thoracic disorders. Recommendations for equipment, initial settings, titration guidelines, monitoring of leak and asynchrony, and follow-up care are provided [20].

Patient-ventilator asynchrony is common in patients treated with NIPPV [21]. Leaks are often a factor and should be monitored closely and corrected as needed [20, 22]. Advanced settings should be matched to the disease mechanics. High trigger sensitivity (degree of inspiratory flow change needed to change the pressure from EPAP to IPAP), longer rise time (time to transition from EPAP to IPAP), longer inspiratory time (Ti), and low cycle sensitivity (levels of inspiratory flow below which device changes from IPAP to EPAP) are generally preferred in restrictive thoracic disorders [1, 23]. These settings allow for less work to trigger supported inspiratory breaths, and allow for maximal alveolar recruitment. Identifying abnormal respiratory events on polysomnography in patients on NIPPV can be challenging, and a systematic description has been proposed [24].

Close follow-up of patients on NIPPV is a recommended best practice to ensure effective utilization (by objective data if possible), to remediate problems, and to ensure adequate equipment maintenance, with periodic assessment of oxygenation and ventilation [22]. An algorithm incorporating simple assessments such as clinical symptoms, daytime $PaCO_2$, nocturnal oximetry, and NIPPV software monitoring has been proposed [25].

Tracheostomy is reserved for severe restrictive lung disorder and chronic respiratory failure with relative contraindication to NIPPV, failed NIPPV, or inability to cooperate with NIPPV treatment. However, to date there are little data regarding the effect these treatments have in chest wall disorders [16, 22].

Surgical treatment in scoliosis may be an option if there is severe deformity with Cobb angle > 45° or those with angle <45° but with physical or functional limitations. The procedures include internal fixation with stainless-steel rods, screws and spinal fusion. Even though the effect of surgery on pulmonary function have been controversial there have been trials showing improvement in Cobb angle and VC after Harington instrumentations [2].

Conclusion

Restriction from kyphoscoliosis is one of the less common causes of hypoventilation that we encounter in our typical practice. However, given the significant consequences that it can have on a patient's breathing (especially during sleep), we should be mindful of this disorder in our sleep related breathing disorder patients.

Clinical Pearls

- Chest wall disorders including scoliosis may be associated with significant hypoxemia and hypercapnia.
- Alveolar hypoventilation is typically worse during sleep than wakefulness, with most impairment apparent during REM sleep.
- Accepted criteria to initiate NIPPV in restrictive thoracic disorders include symptoms, awake hypercapnia, and nocturnal oxygen desaturation by oximetry. Diagnostic polysomnography is not required but may be considered if it would affect management.
- Multiple NIPPV modes are available to treat hypoventilation in restrictive thoracic disorders. While there is no consensus on the best NIPPV modality, it makes sense that these patients may benefit from high trigger sensitivity, longer rise time, longer inspiratory time, and low cycle sensitivity. Therapeutic polysomnography is not necessary but recommended for titration of NIPPV.
- Follow-up of patients on NIPPV includes assessment of symptoms, objective data from NIPPV device, home nocturnal oximetry, and CO_2 monitoring by ABG or noninvasive method if available.

References

1. Selim BJ, Wolfe L, Coleman JM, Dewan NA. Initiation of noninvasive ventilation for sleep related hypoventilation disorders: advanced modes and devices. Chest. 2018;153:251–65.
2. Al-Qadi MO. Disorders of the chest wall: clinical manifestations. Clin Chest Med. 2018;39:361–75.
3. Tzelepis GE. Chest wall diseases: respiratory pathophysiology. Clin Chest Med. 2018;39:281–96.

4. Won CHJ, Kryger M. Sleep in patients with restrictive lung disease. Clin Chest Med. 2014;35:505–12.
5. Böing S, Randerath WJ. Chronic hypoventilation syndromes and sleep-related hypoventilation. J Thorac Dis. 2015;7:1273–85.
6. Branthwaite MA. Cardiorespiratory consequences of unfused idiopathic scoliosis. Br J Dis Chest. 1986;80:360–9.
7. Hilbert J. Sleep-disordered breathing in neuromuscular and chest wall diseases. Clin Chest Med. 2018;39:309–24.
8. Mezon BL, West P, Israels J, Kryger M. Sleep breathing abnormalities in kyphoscoliosis. Am Rev Respir Dis. 1980;122:617–21.
9. Guilleminault C, Kurland G, Winkle R, Miles LE. Severe kyphoscoliosis, breathing, and sleep: the "Quasimodo" syndrome during sleep. Chest. 1981;79:626–30.
10. Midgren B, Petersson K, Hansson L, Eriksson L, Airikkala P, Elmqvist D. Nocturnal hypoxaemia in severe scoliosis. Br J Dis Chest. 1988;82:226–36.
11. Gonzalez C, Ferris G, Diaz J, Fontana I, Nuñez J, Marín J. Kyphoscoliotic ventilatory insufficiency: effects of long-term intermittent positive-pressure ventilation. Chest. 2003;124:857–62.
12. Bergofsky EH. Respiratory failure in disorders of the thoracic cage. Am Rev Respir Dis. 1979;119:643–69.
13. Lisboa C, Moreno R, Fava M, Ferretti R, Cruz E. Inspiratory muscle function in patients with severe kyphoscoliosis. Am Rev Respir Dis. 1985;132:48–52.
14. Kafer ER. Idiopathic scoliosis. Gas exchange and the age dependence of arterial blood gases. J Clin Invest. 1976;58:825–33.
15. Yamane T, Date T, Tokuda M, et al. Hypoxemia in inferior pulmonary veins in supine position is dependent on obesity. Am J Respir Crit Care Med. 2008;178:295–9.
16. Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, and nocturnal hypoventilation—a consensus conference report. Chest. 1999;116:521–34.
17. Ward S, Chatwin M, Heather S, Simonds AK. Randomised controlled trial of non-invasive ventilation (NIV) for nocturnal hypoventilation in neuromuscular and chest wall disease patients with daytime normocapnia. Thorax. 2005;60:1019–24.
18. Arellano-Maric MP, Gregoretti C, Duiverman M, Windisch W. Long-term volume-targeted pressure-controlled ventilation: sense or nonsense? Eur Respir J. 2017;49:1602193.
19. Hess DR. Noninvasive ventilation for neuromuscular disease. Clin Chest Med. 2018;39(2):437–47. Google Search.
20. Kushida CA, Chediak A, Berry RB, et al. Clinical guidelines for the manual titration of positive airway pressure in patients with obstructive sleep apnea. J Clin Sleep Med. 2008;4:157–71.
21. Aboussouan LS. Sleep-disordered breathing in neuromuscular disease. Am J Respir Crit Care Med. 2015;191:979–89.
22. NPPV Titration Task Force of the American Academy of Sleep Medicine. Best clinical practices for the sleep center adjustment of noninvasive positive pressure ventilation (NPPV) in stable chronic alveolar hypoventilation syndromes. J Clin Sleep Med. 2010;6:491–509.
23. Johnson KG, Johnson DC. Treatment of sleep-disordered breathing with positive airway pressure devices: technology update. Med Devices (Auckl). 2015;8:425–37.
24. Gonzalez-Bermejo J, Perrin C, Janssens JP, et al. Proposal for a systematic analysis of polygraphy or polysomnography for identifying and scoring abnormal events occurring during noninvasive ventilation. Thorax. 2012;67:546–52.
25. Janssens J-P, Borel J-C, Pépin J-L. Nocturnal monitoring of home non-invasive ventilation: the contribution of simple tools such as pulse oximetry, capnography, built-in ventilator software and autonomic markers of sleep fragmentation. Thorax. 2011;66:438.

Chapter 15
Postoperative Respiratory Failure

Javier Lorenzo and Anthony G. Doufas

Case Scenario

A 67-year-old man, former smoker, is scheduled for a laparoscopic robotic-assisted prostatectomy. He has a history of chronic obstructive pulmonary disorder (COPD), chronic kidney disease, hypertension, and diabetes controlled on oral agents. The patient is 6 feet tall, weighs 265 pounds, and is endorsed to be a heavy snorer by his spouse. Preoperative labs were unremarkable except for some mild creatinine elevation at 1.45 mg/dL and serum bicarbonate of 30 mEq/L. He is able to climb two flights of stairs without dyspnea or chest pain and has a full neck with a Mallampati class III airway.

On anesthetic induction, although hemodynamically stable, he presents with a rapid desaturation, detected by pulse oximetry. Two-hand bag mask ventilation with an oral airway in place is required for effective ventilation. A video laryngoscope equipped with a size 4 Macintosh blade is needed to intubate the trachea due to poor visualization of the vocal cords. During the case, the patient is placed in steep Trendelenburg position for approximately 3 h. High peak airway pressures were experienced intermittently during surgery, while the ventilator is set at a 20% inspiratory hold (P_{plat} at 30 cmH_2O), positive end-expiratory pressure (PEEP) of 10 cmH_2O, with an oxygen fraction in the inspired gases (FiO_2) of 0.5.

The patient received a total of 2.5 L normosol crystalloid solution and, despite a blood loss of approximately 0.8 L, no blood transfusion was required. At the end of the procedure, a dose of sugammadex was administered to reverse neuromuscular blockade (train-of-four: 4 strong twitch heights by qualitative assessment), and, after extubation of the trachea, he was transported to the post-anesthesia care unit (PACU) on supplemental oxygen. Approximately 20 min after arrival to PACU, a

J. Lorenzo (✉) · A. G. Doufas
Stanford University School of Medicine, Stanford, CA, USA
e-mail: javierl@stanford.edu; agdoufas@stanford.edu

C. Won (ed.), *Complex Sleep Breathing Disorders*,
https://doi.org/10.1007/978-3-030-57942-5_15

desaturation alarm goes off, and the patient is noted to be obtunded and tachycardic. A rapid response team was called, and the trachea was re-intubated to secure the airway and establish effective ventilation and oxygenation. An arterial blood gas analysis before tracheal re-intubation showed: pH: 7.08, $PaCO_2$: 92 mmHg PaO_2: 55 mmHg, and HCO_3: 30 mEq/L.

Discussion

Pulmonary complications after surgery, including atelectasis and pulmonary edema, are common and, when unobserved or left untreated, can culminate in postoperative respiratory failure (PRF), a most devastating outcome. The incidence of PRF in the general surgical population ranges from 0.2% to 3.4%, with a mortality rate that in certain cases can exceed 25% [1–3].

The large heterogeneity of factors contributing to the pathogenesis of PRF, as well as the variable time frame for its occurrence in the postoperative period, complicate a simple unifying definition for this condition. However, most clinicians would recognize it in practice as the failure of gas exchange to meet clinical demand leading to hypoxemia with or without hypercapnia. Clinical signs and arterial blood gas analysis are thus the main criteria for establishing PRF diagnosis, with ventilatory failure indicated by a $PaCO_2$ exceeding 50 mmHg and oxygenation insufficiency by a PaO_2 lower than 60 mmHg (breathing room air at sea level).

In this chapter we will review the pathophysiology implicated in PRF, examine various scoring tools to predict the risk for PRF, and discuss intraoperative and postoperative strategies to reduce such a risk, along with the risk for other pulmonary complications.

Mechanisms of Postoperative Respiratory Failure

The mechanism of PRF is usually multifactorial. Preexisting pulmonary diseases, atelectasis, and restrictive respiratory syndromes are all implicated in the pathogenesis of PRF. On the other hand, certain changes induced by both anesthesia and the surgery can precipitate and/or worsen the impairment in gas exchange associated with PRF. Furthermore, mechanical ventilation when not appropriately titrated, or a high inspired oxygen fraction ($FiO_2 \geq 0.79$) [4], can also injure the heathy lungs and contribute to the development of pulmonary complications, including PRF.

General anesthesia and neuromuscular blockade cause a reduction in muscle tone that leads to a reduction in lung volume and compression of lung structures, including small airways. This in turn results in resorption of alveolar gases and alveolar collapse, causing atelectasis mainly in the dependent parts of the lungs

[5]. The atelectatic portions of the lung and the associated shunt are responsible for the development of the abnormal gas exchange due to ventilation-perfusion mismatch.

Predicting Postoperative Respiratory Failure

Factors associated with the patient's health status, surgical conditions, and type of anesthetic (regional vs. general) determine a baseline risk for PRF. Important patient-related variables include age, functional status, and comorbid conditions such as cardiopulmonary disorders and obstructive sleep apnea. Emergent procedures, thoracic, and upper abdominal surgery with prolonged operative time carry the highest risk. When these conditions are combined with intraoperative insults such as residual neuromuscular blockade and high pulmonary driving pressures, the risk of lung injury, and PRF increases.

Over the years, various scoring instruments have been developed to predict the risk of developing postoperative pulmonary complications [1] and more specifically PRF (Table 15.1) [2, 3, 6]. In a study using the administrative data from the National Veteran Affairs (VA) Surgical Quality Improvement Program, Arozullah and colleagues [2] developed the PRF risk index. However, significant gender and population (sicker VA patients with multiple comorbidities) biases reduced the generalizability of this index to other populations, and the Arozullah's risk index was later re-evaluated in a broader cohort by Johnson and colleagues [3].

Similarly, Gupta and colleagues [6], using data from the American College of Surgeon National Surgery Quality Improvement Program (NSQIP), developed a risk index for PRF, which, as in previous analyses [2, 3], was defined as failure to wean from mechanical ventilation or unplanned re-intubation of the trachea within 48 h of surgery.

A simple prediction tool that relies on easy to obtain bedside variables is the ARISCAT (Assess Respiratory RIsk in Surgical patients in CATalonia) score [1], which was externally validated using a large European database of general surgical cases (PERISCOPE cohort – Prospective Evaluation of a RIsk Score for postoperative pulmonary COmPlications in Europe) [7]. Although the original ARISCAT score broadly defined pulmonary complications as infection, bronchospasm, aspiration pneumonitis, atelectasis, pleural effusions, and respiratory failure, the PERISCOPE cohort [7] stratified the severity of risk into three levels focusing on PRF alone (PERISCOPE-PRF).

Whether a provider uses the ARISCAT [1], PERISCOPE-PRF [7], or a different predictive score [3, 6], it is important to note that variables like advanced age, chronic illness, and patient's frailty are common among all predictive instruments. Furthermore, open abdominal procedures (particularly in upper abdomen), as well thoracic, cardiac, and emergent surgery, carry the most weight.

Table 15.1 Scoring instruments for the prediction of postoperative pulmonary complications, including respiratory failure

Scoring instrument	Study design and patient population	Explanatory variables	Clinical prediction	Quality of prediction
Canet et al. [1]	ARISCAT ($N = 2464$) Prospective multicenter observational cohort of adult patients undergoing non-obstetric surgery procedures under general, neuraxial, or regional anesthesia	Patient-related factors Age > 50 years Baseline SpO_2% Upper respiratory infection within 30 days Hb ≤ 10 g/dL Procedure-related factors Emergency surgery Surgical incision site (upper abdominal vs. intrathoracic) Duration of surgery	Pulmonary complications Respiratory infection Respiratory failure Pleural effusions Atelectasis Pneumothorax Bronchospasm Aspiration pneumonitis	AUC: 0.80
Canet at al [7].	PERISCOPE-PRF ($N = 5384$) Prospective multicenter observational cohort of patients undergoing any surgical procedure under general or regional anesthesia	Patient-related factors Baseline SpO_2% Preoperative respiratory symptoms History of congestive heart failure History of chronic liver disease Procedure-related factors Emergency surgery Surgical incision (upper abdominal vs. intrathoracic) Duration of surgery	Postoperative respiratory failure	AUC: 0.82
Arozullah et al. [2]	Prospective multicenter observational cohort of men undergoing major noncardiac surgery, using data from the VASQIP (Index development sample: $N = 81,719$; validation sample: $N = 99,390$)	Patient-related factors Age > 60 years Functional status History of COPD Albumin < 3.0 g/dL BUN > 30 mg/dL Procedure-related factors Emergency surgery Type of surgery (Abdominal aortic aneurysm, thoracic, neurosurgery, upper abdominal, or peripheral vascular, and neck)	Mechanical ventilation for longer than 48 h, or unplanned re-intubation of the trachea	AUC: 0.834

Table 15.1 (continued)

Scoring instrument	Study design and patient population	Explanatory variables	Clinical prediction	Quality of prediction
Johnson et al. [3]	Prospective multicenter observational cohort using data from NSQIP ($N = 130,359$) Patients having general or vascular procedures performed under general or neuraxial anesthesia	Patient-related factors Age > 65 years ASA physical status History of severe COPD Sepsis Ascites Albumin ≤ 3.5 g/dL Procedure-related factors Emergency surgery Type of surgery (highest risk: mouth, palate vs. hernia)	Mechanical ventilation for longer than 48 h, or unplanned re-intubation of the trachea	AUC: 0.863
Gupta et al. [6]	Prospective multicenter observational cohort using data from NSQIP (Index development sample: $N = 81,719$; validation sample: $N = 99,390$) Patients having cardiac, vascular, orthopedic and general procedures performed under general or neuraxial anesthesia in academic and community hospitals	Patient-related factors Functional status History of severe COPD Sepsis Ascites Albumin ≤3.5 g/dL Procedure-related factors Emergency surgery Type of surgery (highest risk: aortic and hepatobiliary)	Mechanical ventilation for longer than 48 h, or unplanned re-intubation of the trachea within 30 days of surgery	AUC: 0.897

ARISCAT Assess Respiratory RIsk in Surgical patients in CATalonia, *ASA* American Society of Anesthesiologists, *AUC* Area under the receiver operating characteristic curve, *BUN* Blood urea nitrogen, *COPD* Chronic Obstructive Pulmonary Disease, *Hb* Hemoglobin, *NSQIP* American College of Surgeons National Surgical Quality Improvement Project, *PERISCOPE* Prospective Evaluation of a RIsk Score for postoperative pulmonary COmPlications in Europe, *PRF* Postoperative respiratory failure, SpO_2 Oxyhemoglobin saturation by pulse oximetry, *VASQIP* Veterans Administration Surgical Quality Improvement Project

On the World Wide Web (WWW):

ARISCAT: https://www.mdcalc.com/ariscat-score-postoperative-pulmonary-complications

Gupta Score: https://qxmd.com/calculate/calculator_261/postoperative-respiratory-failure-risk-calculator

Obstructive Sleep Apnea and Postoperative Respiratory Failure

Approximately 30% of the general and surgical population suffer from obstructive sleep apnea (OSA) with most of them lacking a formal diagnosis. Large retrospective cohorts support a strong association between a preoperative diagnosis of OSA and postoperative pulmonary complications, including respiratory failure, re-intubation of the trachea within 6 h of surgery, and mechanical ventilation requiring admission to intensive care settings [8].

Opioid-induced ventilatory compromise has been suggested as a likely mechanism for these adverse outcomes, while both OSA and obesity, two highly comorbid conditions, are common among sufferers of postoperative life-threatening opioid-related ventilatory depression. It is noteworthy however that the increased somnolence preceding such critical events, rather than an inherent sensitivity to the respiratory effects of opioids in OSA, might be primarily responsible for the observed ventilatory compromise [9].

Both OSA and obesity have been identified as risk factors for postoperative pulmonary complications [10]. However, due to the high rate of co-occurrence of obesity with OSA, their independent contribution to the development of PRF is difficult to be elucidated.

Regarding the effect of continuous positive airway pressure (CPAP) on postoperative pulmonary outcomes, evidence is inconclusive. A recent meta-analysis of studies evaluating the effect of perioperative CPAP on postoperative outcomes did not find any effect of CPAP on pulmonary complications [11], while the postoperative use of noninvasive ventilation in bariatric patients with OSA did not alter pulmonary outcomes [12]. On the other hand, a large retrospective cohort supports a role for preoperative CPAP treatment on decreasing unplanned re-intubations of the trachea after surgery [13]. Furthermore, prospective evidence supports the postoperative application of CPAP to mitigate opioid-induced ventilatory depression in bariatric patients with OSA [14] and to improve lung mechanics up to 24 h postoperatively [15].

Perioperative Management to Mitigate Postoperative Respiratory Failure

Several studies have examined various intraoperative and postoperative interventions that can range from supplemental oxygen therapy to noninvasive and invasive ventilatory support with the scope of preventing or treating PRF.

Intraoperative Ventilation Management to Prevent Postoperative Respiratory Failure

The reduction in mortality in acute respiratory distress syndrome (i.e., ARDS) with protective ventilation strategies in the intensive care unit has shifted attention to the way anesthesiologist manage ventilation in the operating room. Driven by clinical and experimental studies, tidal volumes during mechanical ventilation have been reduced to limit lung overdistension and ventilator-induced lung injury (i.e., VILI). Several randomized controlled trials have compared conventional ventilation with different protective ventilation strategies, including lower tidal volume [16], higher PEEP [17, 18], and use of recruitment maneuvers, as well as bundles of interventions [16].

In 2013, the IMPROVE trial (Intraoperative PROtective VEntilation) [16] compared a bundled of lung-protective interventions consisting of low tidal volumes (6–8 mL/kg of predicted body weight), PEEP (6–8 cm H_2O), and recruitment maneuvers, versus a conventional approach defined by no-PEEP and tidal volumes of 10–12 mL/kg of predicted body weight. Lung-protective management significantly reduced the occurrence of primary composite outcome that included pulmonary complications (relative risk, 0.40; 95% confidence interval [CI], 0.24–0.68; $P = 0.001$), as well as the need for ventilatory support within the first 7 days after surgery (relative risk, 0.29; 95% CI, 0.14–0.61; $P = 0.001$). However, a significant criticism of the study has been that the conventional management arm (no PEEP and excessive tidal volume) did not mimic standard clinical practice [19]. Furthermore, due to a bundled intervention, it is not uncertain which intervention had the highest contribution to the improved outcome.

A follow up to IMPROVE was the PROVHILO (PROtective Ventilation using HIgh versus LOw PEEP) [17], which randomized non-obese patients to high PEEP (12 cm H_2O) and recruitment maneuvers versus low PEEP (2 cm H_2O) without recruitment maneuvers while keeping tidal volume the same (8 mL/kg of predicted body weight) in both groups. The trial did not show that the use of PEEP was protective against pulmonary complications. These results would suggest that low tidal volumes rather than PEEP combined with lung recruitment maneuvers are responsible for lung protection in the intraoperative period.

Of note, the PROVHILO trial excluded morbidly obese patients (body mass index $\geq$40 kg/m^2) and patients undergoing laparoscopic surgery, two groups that could potentially benefit from the use of PEEP. However, a recent trial (PROtective intraoperative ventilation with higher versus lower levels of positive end-expiratory pressure in oBESE patients, PROBESE) [18], using a similar design, randomized morbidly obese patients to receive higher level of PEEP (12 cm H_2O) with recruitment maneuvers versus a lower PEEP (4 cm H_2O), while keeping tidal volume the same (7 mL/kg of predicted body weight), was not able to demonstrate a difference in the postoperative pulmonary complications, between the two groups.

Residual Neuromuscular Blockade

Residual neuromuscular blockade is a highly prevalent, yet substantially under-recognized complication that has been implicated in the majority of critical respiratory events in the PACU. A recent large retrospective data analysis has demonstrated that the adoption of a qualitative initiative for the perioperative management of neuromuscular blockade significantly decreased the incidence of pulmonary complications (odds ratio 0.73; 95% CI, 0.61–0.88, $P = 0.001$) [20].

The consensus statement for the perioperative use of neuromuscular monitoring [21] advises that clinical signs such as sustained head lift and the time since the last administration of a neuromuscular blocking drug should never dictate the need for reversal and fervently recommends the use of quantitative monitoring of neuromuscular function.

To mitigate the risk of weakness, upper airway obstruction, and/or hypoxemia, a full reversal either with an acetylcholinesterase inhibitor (e.g., neostigmine) or sugammadex, a new selective muscle relaxant binding agent, is recommended whenever neuromuscular blocking drugs are used.

Postoperative Management and Rescue Modalities

The efficacy or noninvasive positive pressure ventilation (NIPPV) in the treatment of PRF has been established [22]. Continuous positive airway pressure and bi-level NIPPV can reduce the work of breathing, improve gas exchange, and recruit atelectatic areas of the lung, while their perioperative use can reduce the rate of tracheal re-intubation, hospital stay, nosocomial infections, and mortality [22]. Postoperative patients should be placed on NIPPV in the early stages of respiratory insufficiency or as a standard practice in high-risk patients. Once respiratory failure impairs sensorium and progresses to cardiac arrest, or if there is emesis or aspiration, NIPPV should be retired for an invasive airway.

A concerning complication from the use of NIPPV after abdominal surgery associated with a proximal gastrointestinal anastomosis is the disruption of the suture line due to gastric/esophageal distention. Jaber and colleagues [23] randomized 300 patients who developed hypoxemic respiratory failure after laparoscopic and open abdominal procedures, to either standard oxygen therapy or NIPPV. The use of NIPPV titrated between 5 and 15 cmH_2O reduced the rate of tracheal re-intubation within 7 days of surgery, from 45.5% in the control group to 33.1% in the treatment group (absolute difference [NIPPV − Standard oxygen therapy], −12.41%; 95% CI, −23.51% to −1.31%, $P = 0.03$). Of note, patients randomized to the NIPPV group included patients who had undergone esophagectomy, gastrectomy, and Whipple procedures, and no adverse events or suture disruption was reported.

High-flow nasal cannula (HFNC) is a relatively new technique with a continuously expanding role in perioperative medicine. These systems deliver warm humidified oxygen via a single-limb circuit with gas flow that can reach up to 60 L/min. Because of high flow rates that can be set to match the peak inspiratory flow of

most patients in respiratory failure, entrainment of room air is limited. In addition, HFNC can generate some flow-dependent continuous positive airway pressure and a reduction in dead space because of upper airway washout, whereby the high-flow oxygen continually displaces carbon dioxide.

The clinical efficacy of HFNC, compared to conventional oxygen therapy and NIPPV, to improve outcomes and reduce the rate tracheal re-intubation has been demonstrated in critical care patients suffering from hypoxemic respiratory failure [24, 25]. However, the role of HFNC in treating PRF and preventing tracheal re-intubation after surgery, compared to other therapeutic modalities, like supplemental oxygen therapy or NIPPV, remains unclear [25]. Stephane and colleagues showed in a large randomized trial of 830 patients that HFNC was not inferior to NIPPV in the treatment of hypoxemic respiratory failure in post-cardiac surgery patients [26]. Of note, the average $PaCO_2$ levels were normal at 39 mmHg at baseline in both groups, so the utility of HFNC in rescuing PRF with hypercapnia is not as clear.

Conclusion

Besides respiratory failure, postoperative pulmonary complications include pneumonia, atelectasis, bronchospasm, pneumothorax, pleural effusions, aspiration pneumonia/pneumonitis, and prolonged mechanical ventilation. Postoperative respiratory failure remains a devastating complication that occurs in the general surgical population with an incidence between 0.2% and 3.4% and a mortality rate as high as 25%. It results from several interacting factors, including patient health status, surgical insult, and intraoperative events. With careful screening, using available predictive instruments, the adequate resource utilization can improve outcomes. Attention to careful implementation of evidence-based measures to reduce PRF should guide local practice. As it stands, PRF is a quality and patient safety indicator that must be reported to several agencies such as the Agency for Healthcare Research and Quality (AHRQ).

Clinical Pearls

- Postoperative respiratory failure (PRF) has a high mortality. The incidence of PRF in the general surgical population ranges from 0.2% to 3.4%, with a mortality rate that in certain cases can exceed 25%.
- Individual risk for PRF can be estimated with clinical predictive scores. Factors associated with the patient's health status, surgical conditions, and type of anesthetic (e.g., regional vs. general) determine a baseline risk for PRF.
- Intraoperative protective ventilation with low tidal volume and driving pressure have been found to reduce the incidence of postoperative pulmonary complications.

- Noninvasive ventilation has an important role in the treatment of postoperative pulmonary complications, including respiratory failure. Continuous positive airway pressure and bi-level NIPPV can reduce the work of breathing, improve gas exchange, and recruit atelectatic areas of the lung, while their perioperative use can reduce the rate of tracheal re-intubation, hospital stay, nosocomial infections, and mortality. Postoperative patients should be placed on NIPPV in the early stages of respiratory insufficiency, or as a standard practice in high-risk patients.

References

1. Canet J, Gallart L, Gomar C, et al. Prediction of postoperative pulmonary complications in a population-based surgical cohort. Anesthesiology. 2010;113(6):1338–50.
2. Arozullah AM, Daley J, Henderson WG, Khuri SF. Multifactorial risk index for predicting postoperative respiratory failure in men after major noncardiac surgery. The National Veterans Administration Surgical Quality Improvement Program. Ann Surg. 2000;232(2):242–53.
3. Johnson RG, Arozullah AM, Neumayer L, Henderson WG, Hosokawa P, Khuri SF. Multivariable predictors of postoperative respiratory failure after general and vascular surgery: results from the patient safety in surgery study. J Am Coll Surg. 2007;204(6):1188–98.
4. Staehr-Rye AK, Meyhoff CS, Scheffenbichler FT, et al. High intraoperative inspiratory oxygen fraction and risk of major respiratory complications. Br J Anaesth. 2017;119(1):140–9.
5. Di Marco F, Bonacina D, Vassena E, et al. The effects of anesthesia, muscle paralysis, and ventilation on the lung evaluated by lung diffusion for carbon monoxide and pulmonary surfactant protein B. Anesth Analg. 2015;120(2):373–80.
6. Gupta H, Gupta PK, Fang X, et al. Development and validation of a risk calculator predicting postoperative respiratory failure. Chest. 2011;140(5):1207–15.
7. Canet J, Sabate S, Mazo V, et al. Development and validation of a score to predict postoperative respiratory failure in a multicentre European cohort: a prospective, observational study. Eur J Anaesthesiol. 2015;32(7):458–70.
8. Mokhlesi B, Hovda MD, Vekhter B, Arora VM, Chung F, Meltzer DO. Sleep-disordered breathing and postoperative outcomes after elective surgery: analysis of the nationwide inpatient sample. Chest. 2013;144(3):903–14.
9. Doufas AG, Shafer SL, Rashid NHA, Kushida CA, Capasso R. Non-steady state modeling of the ventilatory depressant effect of remifentanil in awake patients experiencing moderate-to-severe obstructive sleep apnea. Anesthesiology. 2019;130(2):213–26.
10. Malcolm TL, Knezevic NN, Zouki CC, Tharian AR. Pulmonary complications after hip and knee arthroplasty in the United States, 2004-2014. Anesth Analg. 2019;130:917–24.
11. Nagappa M, Mokhlesi B, Wong J, Wong DT, Kaw R, Chung F. The effects of continuous positive airway pressure on postoperative outcomes in obstructive sleep apnea patients undergoing surgery: a systematic review and meta-analysis. Anesth Analg. 2015;120(5):1013–23.
12. Stefan MS, Hill NS, Raghunathan K, et al. Outcomes associated with early postoperative noninvasive ventilation in bariatric surgical patients with sleep apnea. J Clin Sleep Med. 2016;12(11):1507–16.
13. Abdelsattar ZM, Hendren S, Wong SL, Campbell DA Jr, Ramachandran SK. The impact of untreated obstructive sleep apnea on cardiopulmonary complications in general and vascular surgery: a cohort study. Sleep. 2015;38(8):1205–10.

14. Zaremba S, Shin CH, Hutter MM, et al. Continuous positive airway pressure mitigates opioid-induced worsening of sleep-disordered breathing early after bariatric surgery. Anesthesiology. 2016;125(1):92–104.
15. Neligan PJ, Malhotra G, Fraser M, et al. Continuous positive airway pressure via the Boussignac system immediately after extubation improves lung function in morbidly obese patients with obstructive sleep apnea undergoing laparoscopic bariatric surgery. Anesthesiology. 2009;110(4):878–84.
16. Futier E, Constantin JM, Paugam-Burtz C, et al. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. N Engl J Med. 2013;369(5):428–37.
17. PROVE Network Investigators, Hemmes SNT, de Abreu MG, Pelosi P, Schultz MJ. High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicentre randomised controlled trial. Lancet. 2014;384(9942):495–503.
18. Writing Committee for the PROBESE Collaborative Group of the PROtective VEntilation Network (PROVEnet) for the Clinical Trial Network of the European Society of Anaesthesiology, Bluth T, Serpa Neto A, Schultz MJ, Pelosi P, Gama de Abreu M. Effect of intraoperative high positive end-expiratory pressure (PEEP) with recruitment maneuvers vs low PEEP on postoperative pulmonary complications in obese patients: a randomized clinical trial. JAMA. 2019;18:2292–305.
19. Guldner A, Kiss T, Serpa Neto A, et al. Intraoperative protective mechanical ventilation for prevention of postoperative pulmonary complications: a comprehensive review of the role of tidal volume, positive end-expiratory pressure, and lung recruitment maneuvers. Anesthesiology. 2015;123(3):692–713.
20. Rudolph MI, Chitilian HV, Ng PY, et al. Implementation of a new strategy to improve the perioperative management of neuromuscular blockade and its effects on postoperative pulmonary complications. Anaesthesia. 2018;73(9):1067–78.
21. Naguib M, Brull SJ, Kopman AF, et al. Consensus statement on perioperative use of neuromuscular monitoring. Anesth Analg. 2018;127(1):71–80.
22. Faria DA, da Silva EM, Atallah AN, Vital FM. Noninvasive positive pressure ventilation for acute respiratory failure following upper abdominal surgery. Cochrane Database Syst Rev. 2015;10:CD009134.
23. Jaber S, Lescot T, Futier E, et al. Effect of noninvasive ventilation on tracheal reintubation among patients with hypoxemic respiratory failure following abdominal surgery: a randomized clinical trial. JAMA. 2016;315(13):1345–53.
24. Hernandez G, Vaquero C, Gonzalez P, et al. Effect of postextubation high-flow nasal cannula vs conventional oxygen therapy on reintubation in low-risk patients: a randomized clinical trial. JAMA. 2016;315(13):1354–61.
25. Huang HW, Sun XM, Shi ZH, et al. Effect of high-flow nasal cannula oxygen therapy versus conventional oxygen therapy and noninvasive ventilation on reintubation rate in adult patients after extubation: a systematic review and meta-analysis of randomized controlled trials. J Intensive Care Med. 2018;33(11):609–23.
26. Stephan F, Barrucand B, Petit P, et al. High-flow nasal oxygen vs noninvasive positive airway pressure in hypoxemic patients after cardiothoracic surgery: a randomized clinical trial. JAMA. 2015;313(23):2331–9.

Chapter 16
Sleep Disordered Breathing at High Altitude

Gabriel Anders and Bernardo J. Selim

Clinical Presentation

R. P. is a 64-year-old morbidly obese male (BMI of 30 kg/m^2) with a previous history of hypertension, type 2 diabetes mellitus, and depression who presents to a sleep medicine clinic in Flagstaff, Arizona (6910 feet / 2106 m), where he was vacationing in his timeshare. He was previously diagnosed with non-positional obstructive sleep apnea in Washington D.C. (410 feet / 125 m) 3 years previously. At that time, his split night in-lab polysomnography showed an overall apnea-hypopnea index (AHI) of 27 events/h consisting of only obstructive apneas and hypopneas during a total sleep time of 123 min in the diagnostic portion. Optimal continuous positive airway pressure (CPAP) titration was reached at 12 cmH_2O.

He presents to the sleep medicine clinic in Flagstaff, Arizona, complaining of excessive daytime sleepiness, frequent awakenings with feelings of suffocation at night, and witnessed apneas while wearing his CPAP device. These symptoms are only present during his vacation time in Flagstaff, resolving every time upon returning home (Washington D.C.).

Download of his CPAP device shows that prior to going on vacation, his residual AHI was 2.7 events per hour (only hypopneas) with an average usage of 8 h and 34 min. Over the past 4 days, he has been at Flagstaff, his download shows a

G. Anders
Division of Pulmonary, Sleep and Critical Care Medicine, University of Missouri-Kansas City, Kansas City, MO, USA

B. J. Selim (✉)
Mayo Clinic Center for Sleep Medicine, Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA
e-mail: selim.bernardo@mayo.edu

C. Won (ed.), *Complex Sleep Breathing Disorders*,
https://doi.org/10.1007/978-3-030-57942-5_16

residual AHI of 23 events/h, with predominately central apneas. He maintained minimal mask leak throughout utilizing a nasal mask interface; however the amount of periodic breathing during the night significantly increased (Fig. 16.1). Overnight oximetry is performed, and results are shown in Fig. 16.2. He is asking what additional treatments can be done to help his symptoms.

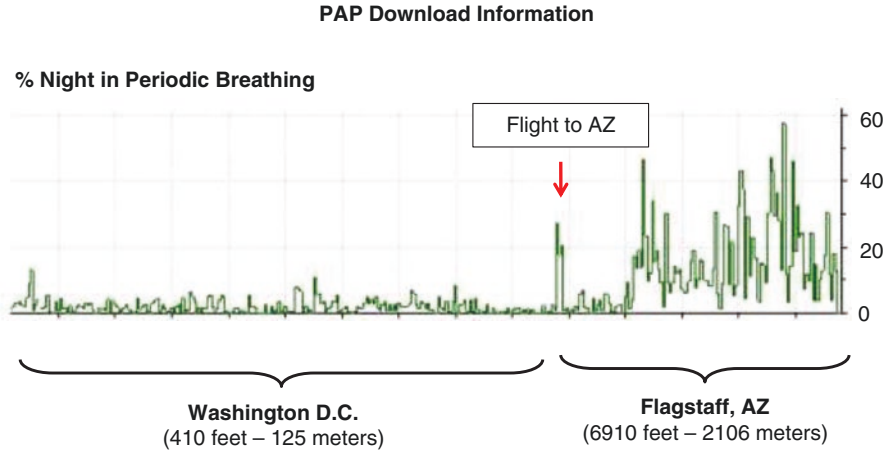


Fig. 16.1 Change in percentage of nocturnal periodic breathing from Washington D.C. to Flagstaff, Arizona, on PAP download

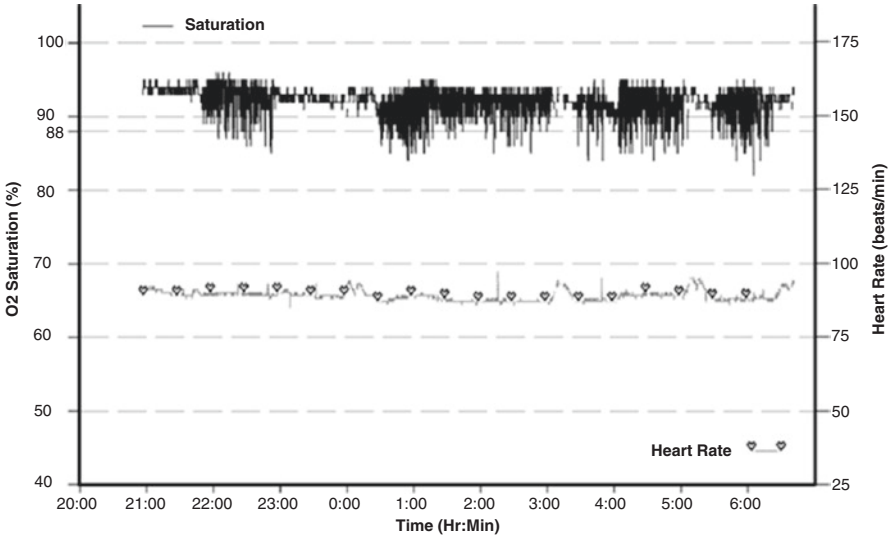


Fig. 16.2 Overnight oximetry obtained after traveling to Flagstaff, AZ, showing frequent oscillatory desaturations

Discussion

High-altitude periodic breathing is characterized by alternating periods of absent respiratory efforts (i.e., central sleep apnea (CSA)) with periods of hyperventilation (hyperpnea) in the absence of other etiologies of periodic breathing (e.g., congestive heart failure with Cheyne-Stokes breathing or intake of narcotics) [1]. High-altitude periodic breathing is a common response to altitude – becoming more common with higher elevations and almost ubiquitous at altitudes >4000 m. There is no level of central AHI that is considered an "abnormal" response. It is the presence of associated symptoms that make the findings of central apneas at altitude considered a disorder. Patients may complain of excessive daytime sleepiness, sleep fragmentation (insomnia), gasping awake, morning headaches, and dyspnea.

The elevation, speed of the ascent, and individual predisposition may play an important role in the pathogenesis of high-altitude periodic breathing. The more rapid the ascent and the higher the altitude, the greater the risk of developing periodic breathing. Descending to a lower altitude will often relieve central apneas [2]. Periodic breathing may develop during ascension, immediately after or during the acclimatization period. Few individuals exhibit periodic breathing at altitudes as low as 1500 m (4900 feet), while up to 25% will develop it at 2500 m (8202 feet), and as mentioned, virtually everyone at 4000 m (13,000 feet) will develop some degree of high-altitude periodic breathing [3]. Periodic breathing can also be observed in those individuals chronically living and acclimatized to high altitude (i.e., highlanders). In comparison to individuals living at sea level, highlanders living at an altitude of 3825 m have a greater prevalence of sleep apnea (77% vs 54%, $p < 0.001$), as well as a twofold increase in sleep apnea severity, largely explained by increased frequency of central rather than obstructive events [4].

Pathophysiologic effects of high altitude relate to changes in barometric pressure and subsequent changes in the ambient pressure of oxygen. Since the fraction of inspired oxygen remains constant at approximately 21% during ascension, the most important determinant of arterial oxygen tension (PaO_2) at any altitude is the barometric pressure. For example, at an altitude of 3000 m, the barometric pressure and inspired atmospheric partial pressure of oxygen is only about 70% of that at sea level. As PaO_2 falls due to a low atmospheric pressure (hypobaric hypoxia) upon ascension, ventilation will be stimulated resulting in hypocapnia and respiratory alkalosis. The magnitude of the ventilatory response increases with increasing altitude and progresses over days after ascension. It is this hyperventilation triggered by hypoxia, with subsequent fall in arterial carbon dioxide ($PaCO_2$) below the apneic threshold, that results in central apneas [5]. With breathing cessation, increased $PaCO_2$ will trigger a subsequent hyperventilation period with high tidal volumes, in which the PaO_2 rises and $PaCO_2$ falls to near wakefulness level, perpetuating the respiratory oscillation (periodic breathing). Even though acclimatization to high altitude results in an overall increase in saturation of oxygen (SpO_2), periodic breathing may still increase in duration and persist in time as a result of the

progressive increase in the respiratory control system response to hypoxia and hypercapnia (i.e., a high loop gain) [1, 6, 7].

Sex differences in the propensity for high-altitude periodic breathing have been noted. Women stabilize their respiration at high altitude more quickly than do men and demonstrate less proclivity for central apneas [17]. It is thought that women may be protected due to the effect of estrogen and/or progesterone; however, the exact mechanism remains unclear. Women may have a blunted hypoxic ventilatory response that protects them against hyperventilation and subsequent hypocapnia-induced central apneas (i.e., lower loop gain). In addition, heritable genetic variability in ventilatory chemo-responsiveness has been shown, though whether the propensity for developing high-altitude periodic breathing is also inherited is unknown [4]. Persons who have developed high-altitude periodic breathing in the past are more likely to have recurrence upon re-ascension, and therefore these patients deserve prophylactic therapies and closer follow-up.

On polysomnography, central apneas occur during non-rapid eye movement (NREM) sleep while being largely absent during rapid eye movement (REM) sleep. This is thought to be due to the fact that the primary driver of ventilation during NREM sleep is chemo-responsiveness, while hypoxic and hypercapnic responsiveness is blunted during REM sleep. Central apneas are generally short (cycles lengths <40 s) in high-altitude periodic breathing, unlike that seen with Cheyne-Stokes respiration related to heart failure. Sleep is often disrupted, though overall total sleep time and REM time may be preserved.

Among patients with known obstructive sleep apnea (OSA), exposure to high altitude may cause worsening of sleep disordered breathing by worsening obstructive events or by inducing central events [8, 9]. Independent of sex, patients with cardiovascular disease are at increased risk for obstructive sleep apnea and central sleep apnea at high altitude [10]. In lifelong altitude residents with severe pulmonary hypertension associated with excessive erythrocytosis (i.e., chronic mountain sickness), central and obstructive apneas, as well as nocturnal hypoxemia, have shown to be more severe compared with healthy high-altitude dwellers [2]. In patients with OSA who travel to high altitude (e.g., 2750 m), their home positive airway pressure (PAP) settings may be inadequate to treat their obstructive sleep apnea. Although application of positive airway pressure is associated with decreased central sleep apnea and hypoxemia that occurs with altitude, baseline PAP settings may be suboptimal to completely eliminate OSA, resulting in higher sleep apnea severity and sleep fragmentation [11]. The fan speeds in CPAP machines need to adjust for barometric pressure change in order to keep the delivered CPAP pressure consistent at different altitudes. Newer machines are able to automatically adjust to altitude, while older machines need to be manually adjusted.

In the above clinical case, it appears the patient's sleep-related symptoms emerge in Flagstaff, Arizona. The altitude of Flagstaff, Arizona, is 2106 m in comparison to the altitude of Washington D.C at 125 m. By physiologic adaptation of oxygen content and oxygen carrying capacity to high altitude, slow ascent can decrease respiratory drive triggered by hypoxia. Therefore, slow ascension and subsequent acclimatization are among several interventions to ameliorate the development of

sleep related breathing disorders. Unfortunately, at elevations above 3500–4000 m, acclimatization alone does not restore normal sleep or prevent the development of CSA. There are a few evidence-based options to treat this patient. If descending from high altitude is not an option, adjunctive treatment with acetazolamide and/or oxygen has been proven to be effective measures; however, availability, side effects, and limitations of the intervention should be cautiously considered.

Acetazolamide improves sleep apnea at high altitude by inducing a metabolic acidosis and behaving as a respiratory stimulant. Acetazolamide has shown to decrease AHI, decrease percentage of periodic breathing time, and increase nocturnal oxygenation in patients with high-altitude periodic breathing [12]. In the current literature, acetazolamide dosing has ranged anywhere from a daily dose of 250–750 mg; however, prophylactic dose of 125–250 mg by mouth twice daily is currently recommended to be started anywhere from 1 to 3 days prior to ascent [13, 14]. If the patient has a previously diagnosed sleep disorder, it is highly encouraged to continue PAP therapy while at high altitude [13]. Data has shown that patients with OSA who spend 3 days at moderately elevated altitude, a combination of both acetazolamide and auto-CPAP, compared with auto-CPAP alone, was superior at improving nocturnal SpO_2 and AHI [15]. Alternatively, because hypoxia is the main mechanism driving periodic CSA at high altitude, supplementing oxygen (1–2 L/min, or at a rate that results in $SpO_2 > 90\%$) to CPAP may suppress high-altitude periodic CSA in patients with obstructive sleep apnea [3]. In a small study of previously healthy individuals, supplemental oxygen alone was shown to be superior to adaptive servo-ventilation (ASV) in periodic breathing at high altitude [16]. When feasible, however, descending from altitude is always the treatment of choice.

As in our patient, it may be beneficial to obtain download data in patients who are not acclimatized to taking short trips at high altitudes [14]. A brief download of the patient's PAP device at high altitude can delineate what types of events are happening (e.g., uncontrolled OSA vs emergent CSA). If there is underlying lung disease present, a high-altitude simulation test can be performed to determine if the patient needs supplemental oxygen. At the current time, there is no mechanism to perform a simulated high-altitude polysomnogram unless the sleep center is at the desired altitude where the patient will be traveling. For patients who live at altitude and are getting sleep studies at sea level, a false-negative study may result since AHI decreases significantly with descent [17]. Although there are no guidelines or consensus regarding adjustment of PAP therapy during ascension, it is important to recommend PAP adherence to individuals with OSA who travel to and sleep at higher altitudes. Current data support that baseline PAP settings may be inadequate to eliminate hypopneas at high altitude. Although we may speculate that variable pressure or auto-PAP devices might adequately treat OSA at high altitude, decisions regarding escalation of PAP therapy for such patients may need to be made on a case-by-case basis based on suspected predominant type of breathing disorder. The addition of low flow oxygen entrained into the PAP device may also be considered based on feasibility and availability of location.

In addition to periodic breathing at high altitude, there is also a growing body of literature on acute mountain sickness (AMS) and the benefit of CPAP therapy. AMS

happens typically when a fall of barometric pressure upon ascension results in hypoxia-driven symptoms such as high-altitude cerebral edema with altered mental status, headache, ataxia, fatigue, nausea, vomiting, and high-altitude pulmonary edema (HAPE). It should be noted that high-altitude periodic breathing is *not* the same as nor a form of acute or chronic mountain sickness (Table 16.1). Periodic breathing is a common response to altitude that affects virtually all persons at >4000 m [18]. Whether proclivity or severity of periodic breathing predicts or predisposes to AMS has been evaluated. The AHI that results from high-altitude periodic breathing does not differ between those who do and do not develop AMS at >4000 m. However, those who develop AMS tend to have markedly worse nocturnal and wake SpO_2. It is unclear whether high-altitude sleep-breathing disorder contributes to the development of AMS in some individuals, or whether periodic breathing and hypoxemia develop because of the development of HAPE. The current data suggest the latter. It has been suggested that high-altitude periodic breathing may even be protective from AMS and HAPE, since those who readily develop high-altitude periodic breathing have greater hypoxic ventilatory response [8]. This robust hypoxic ventilatory response prevents exaggerated or prolonged oxygen desaturations that would be seen with acute or chronic mountain sickness. In any case, individuals who have a history of periodic breathing or AMS/HAPE are at risk

Table 16.1 Notable differences in acute and chronic mountain sickness

	Acute mountain sickness	Chronic mountain sickness
Timing	Onset within hours and lasts days	Months to years
Altitude	>2400 m	>2500 m (long-term residents)
Symptoms	Headache, dizziness, palpitations, insomnia, loss of appetite, nausea, altered mental status, lightheaded, hallucinations	Cyanosis, malaise, fatigue, exercise intolerance, vein dilation, headache, tinnitus, paresthesia, sleep disturbances
Mechanism	Relative hypoventilation, impaired gas exchange, fluid retention and redistribution, and increased sympathetic drive [20, 21]	Maladaptive ventilator response to high altitude (impaired hypoxemic ventilatory response), abnormal baroreceptor-mediated control of vascular resistance and hypoxemia driven erythropoiesis [22–24]
Complications	High-altitude pulmonary edema, High-altitude cerebral edema, death	Pulmonary hypertension, polycythemia, right ventricular hypertrophy, right heart failure, neuropsychiatric symptoms, peripheral arterial pressure falls, death
Treatment	Descend from altitude, acetazolamide	Descend from altitude, mild exercise, acetazolamide, almitrine, enalapril, medroxyprogesterone
Prevention	Acetazolamide, dexamethasone, ibuprofen, acclimatization, benzodiazepines, avoid smoking and alcohol	None studied

for recurrence upon re-ascension and will benefit from prophylactic treatment. As mentioned, acetazolamide and supplemental oxygen may help with periodic breathing and can also help prevent high-altitude pulmonary edema. Likewise, dexamethasone prior to ascension decreases the likelihood of AMS and HAPE. Dexamethasone may alter sleep architecture but has not shown to change overall periodic breathing AHI [18]. Finally, CPAP therapy is used for high-altitude periodic breathing and may also provide benefit for AMS, likely via improving oxygenation. CPAP use intermittently during wake and during sleep at altitude improved symptoms of AMS and decreased occurrence of HAPE [19].

Clinical Pearls

- Periodic breathing and central sleep apnea develop commonly upon ascending to high altitude due to low barometric pressure resulting in hypobaric hypoxemia due to decreased partial pressure of oxygen.
- Patients with obstructive sleep apnea who were previously asymptomatic may develop daytime sleepiness, sleep fragmentation (insomnia), and sense of dyspnea secondary to worsening OSA, or emergence of high-altitude related periodic breathing.
- If descending from high altitude is not feasible, treatment of symptomatic periodic breathing that develops at altitude includes acetazolamide, continuation of PAP therapy for previously diagnosed sleep disordered breathing, and oxygen supplementation at 1–2 L/min.
- ASV therapy has not been shown to be superior to oxygen supplementation in central sleep apnea due to high-altitude periodic breathing.
- Despite limited published data, acetazolamide therapy is recommended prophylactically for those susceptible to periodic breathing at high altitude at a dose of 125–250 mg by mouth twice daily to be started about 1–3 days prior to ascension.

References

1. Insalaco G, Romano S, Salvaggio A, Pomidori L, Mandolesi G, Cogo A. Periodic breathing, arterial oxyhemoglobin saturation, and heart rate during sleep at high altitude. High Alt Med Biol. 2012;13(4):258–62.
2. Rexhaj E, Rimoldi SF, Pratali L, Brenner R, Andries D, Soria R, et al. Sleep-disordered breathing and vascular function in patients with chronic mountain sickness and healthy high-altitude dwellers. Chest. 2016;149(4):991–8.
3. Burgess KR, Ainslie PN. Central sleep apnea at high altitude. Adv Exp Med Biol. 2016;903:275–83.
4. Pham LV, Meinzen C, Arias RS, Schwartz NG, Rattner A, Miele CH, et al. Cross-sectional comparison of sleep-disordered breathing in native Peruvian highlanders and lowlanders. High Alt Med Biol. 2017;18(1):11–9.
5. Smith CA, Chenuel BJ, Henderson KS, Dempsey JA. The apneic threshold during non-REM sleep in dogs: sensitivity of carotid body vs. central chemoreceptors. J Appl Physiol (1985). 2007;103(2):578–86.

6. Nussbaumer-Ochsner Y, Ursprung J, Siebenmann C, Maggiorini M, Bloch KE. Effect of short-term acclimatization to high altitude on sleep and nocturnal breathing. Sleep. 2012;35(3):419–23.
7. Bloch KE, Latshang TD, Turk AJ, Hess T, Hefti U, Merz TM, et al. Nocturnal periodic breathing during acclimatization at very high altitude at Mount Muztagh Ata (7,546 m). Am J Respir Crit Care Med. 2010;182(4):562–8.
8. Hohenhaus E, Paul A, McCullough RE, Kucherer H, Bartsch P. Ventilatory and pulmonary vascular response to hypoxia and susceptibility to high altitude pulmonary oedema. Eur Respir J. 1995;8(11):1825–33.
9. Nussbaumer-Ochsner Y, Schuepfer N, Ulrich S, Bloch KE. Exacerbation of sleep apnoea by frequent central events in patients with the obstructive sleep apnoea syndrome at altitude: a randomised trial. Thorax. 2010;65(5):429–35.
10. Otero L, Hidalgo P, Gonzalez R, Morillo CA. Association of cardiovascular disease and sleep apnea at different altitudes. High Alt Med Biol. 2016;17(4):336–41.
11. Nishida K, Lanspa MJ, Cloward TV, Weaver LK, Brown SM, Bell JE, et al. Effects of positive airway pressure on patients with obstructive sleep apnea during acute ascent to altitude. Ann Am Thorac Soc. 2015;12(7):1072–8.
12. Liu HM, Chiang IJ, Kuo KN, Liou CM, Chen C. The effect of acetazolamide on sleep apnea at high altitude: a systematic review and meta-analysis. Ther Adv Respir Dis. 2017;11(1):20–9.
13. Nussbaumer-Ochsner Y, Latshang TD, Ulrich S, Kohler M, Thurnheer R, Bloch KE. Patients with obstructive sleep apnea syndrome benefit from acetazolamide during an altitude sojourn: a randomized, placebo-controlled, double-blind trial. Chest. 2012;141(1):131–8.
14. Stadelmann K, Latshang TD, Nussbaumer-Ochsner Y, Tarokh L, Ulrich S, Kohler M, et al. Impact of acetazolamide and CPAP on cortical activity in obstructive sleep apnea patients. PLoS One. 2014;9(4):e93931.
15. Latshang TD, Nussbaumer-Ochsner Y, Henn RM, Ulrich S, Lo Cascio CM, Ledergerber B, et al. Effect of acetazolamide and autoCPAP therapy on breathing disturbances among patients with obstructive sleep apnea syndrome who travel to altitude: a randomized controlled trial. JAMA. 2012;308(22):2390–8.
16. Orr JE, Heinrich EC, Djokic M, Gilbertson D, Deyoung PN, Anza-Ramirez C, et al. Adaptive servoventilation as treatment for central sleep apnea due to high-altitude periodic breathing in nonacclimatized healthy individuals. High Alt Med Biol. 2018;19:178–84.
17. Patz DS, Swihart B, White DP. CPAP pressure requirements for obstructive sleep apnea patients at varying altitudes. Sleep. 2010;33(5):715–8.
18. Nussbaumer-Ochsner Y, Schuepfer N, Ursprung J, Siebenmann C, Maggiorini M, Bloch KE. Sleep and breathing in high altitude pulmonary edema susceptible subjects at 4,559 meters. Sleep. 2012;35(10):1413–21.
19. Johnson PL, Johnson CC, Poudyal P, Regmi N, Walmsley MA, Basnyat B. Continuous positive airway pressure treatment for acute mountain sickness at 4240 m in the Nepal Himalaya. High Alt Med Biol. 2013;14(3):230–3.
20. Moore LG, Harrison GL, McCullough RE, McCullough RG, Micco AJ, Tucker A, et al. Low acute hypoxic ventilatory response and hypoxic depression in acute altitude sickness. J Appl Physiol (1985). 1986;60(4):1407–12.
21. Hackett PH, Rennie D, Hofmeister SE, Grover RF, Grover EB, Reeves JT. Fluid retention and relative hypoventilation in acute mountain sickness. Respiration. 1982;43(5):321–9.
22. Leon-Velarde F, Gamboa A, Rivera-Ch M, Palacios JA, Robbins PA. Selected contribution: peripheral chemoreflex function in high-altitude natives and patients with chronic mountain sickness. J Appl Physiol (1985). 2003;94(3):1269–78; discussion 53–4.
23. Leon-Velarde F, Richalet JP. Respiratory control in residents at high altitude: physiology and pathophysiology. High Alt Med Biol. 2006;7(2):125–37.
24. Moore JP, Claydon VE, Norcliffe LJ, Rivera-Ch MC, Leon-Velarde F, Appenzeller O, et al. Carotid baroreflex regulation of vascular resistance in high-altitude Andean natives with and without chronic mountain sickness. Exp Physiol. 2006;91(5):907–13.

Chapter 17
Congenital Central Hypoventilation Syndrome (CCHS)

Susan M. Slattery, Stephanie M. Marshall, Ilya Khaytin, and Debra E. Weese-Mayer

Case

This case is a former late preterm male infant born at 36 weeks and 5 days gestational age to a 36-year-old mother via *in vitro* fertilization. Pregnancy was complicated by maternal cholestasis of pregnancy, advanced maternal age, and fetal renal pelviectasis. At delivery, infant had presumed secondary apnea after crying vigorously and becoming apneic at 1 minute of life. After 30 seconds of bag-mask ventilation and suctioning, he was vigorous, but remained dusky requiring supplemental

S. M. Slattery (✉)
Division of Pediatric Autonomic Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago and Stanley Manne Children's Research Institute, Chicago, IL, USA

Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Division of Neonatology, Ann & Robert H. Lurie Children's Hospital of Chicago and Stanley Manne Children's Research Institute, Chicago, IL, USA
e-mail: sslattery@luriechildrens.org

S. M. Marshall

Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Division of Neonatology, Ann & Robert H. Lurie Children's Hospital of Chicago and Stanley Manne Children's Research Institute, Chicago, IL, USA
e-mail: smarshall@luriechildrens.org

I. Khaytin
Division of Pediatric Autonomic Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago and Stanley Manne Children's Research Institute, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
e-mail: ikhaytin@luriechildrens.org

D. E. Weese-Mayer
Division of Neonatology, Ann & Robert H. Lurie Children's Hospital of Chicago and Stanley Manne Children's Research Institute, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
e-mail: dweese-mayer@luriechildrens.org, d-weese-mayer@northwestern.edu

C. Won (ed.), *Complex Sleep Breathing Disorders*,
https://doi.org/10.1007/978-3-030-57942-5_17

oxygen. He was admitted into the Neonatal Intensive Care Unit for presumed respiratory distress syndrome related to prematurity. The infant required high-flow nasal cannula support with low oxygen supplementation (up to 30% F_iO_2). At day two of life, he had one prolonged apnea event (at least 30 seconds duration) with a peripheral pulse oximetry-measured oxygen saturation (SpO_2) nadir of 40%, then subsequent bradycardia (heart rate (HR) less than 60 bpm) that necessitated chest compressions for 30 seconds and positive pressure bag-mask ventilation for 2 minutes, with "prompt" recovery. Infant was also given a loading dose of caffeine and had video electroencephalogram (with no documented seizure activity).

Besides his cardiorespiratory history, the infant's course was notable for lack of stool output within the first 48 hours of life and feeding intolerance. With the initiation of enteral feeding, he developed emesis and abdominal distension; moderate dilation of bowel loops were reported on radiographic evaluation. The infant underwent abdominal decompression with a Replogle tube and had a lower gastrointestinal tract contrast enema study to evaluate for stool retention or obstruction. The contrast study revealed a normal caliber rectosigmoid colon, no mucous plug, and the passage of a moderate amount of stool during the study. Rectal irrigations were initiated with minimal stool output and the infant was transferred to a pediatric hospital for the evaluation of possible Hirschsprung disease.

The infant remained on low-flow nasal cannula upon hospital transfer at one week of age. Upon arrival, his exam was notable for small but reactive pupils, comfortable breathing with intermittent mild desaturations (SpO_2 nadir 90%), mild abdominal distention with bowel sounds present, and low-normal central tone. His vital signs showed a broad range of HR, often higher than normal for age, with limited HR variability by beat-to-beat measure. His blood pressures were normal for age and he maintained normal core temperatures without supplemental heat.

Central venous access was obtained upon arrival at the quaternary care center, with the aim to provide nutrition while establishing enteral feeds. Two days after initiating enteral feeds, the patient developed abdominal distension that escalated with feeding advancement over the next 48 hours. A suction rectal biopsy confirmed the absence of ganglion cells, and the diagnosis of Hirschsprung disease. A laparoscopic leveling colostomy with mucous fistula was performed at the level of the descending colon/sigmoid colon junction. A gastrostomy tube was also placed, and postoperative rectal irrigations were resumed with enteral feedings. Attempts at oral feeding led to desaturation events (SpO_2 nadir 75%), likely due to poor coordination of suck/swallow and breathing patterns. A swallow study confirmed esophageal dysmotility. A genetic microarray was ordered to evaluate for genetic aberrations that might account for the infant's unique constellation of symptoms.

Serial evaluations of the infant's respiratory status throughout the admission indicated cardiorespiratory instability. Specifically, after initial hospital transfer on 1 LPM nasal cannula, the low level of support was removed and the infant exhibited frequent self-resolving desaturation events (SpO_2 nadir 75%) awake and asleep. The nasal cannula was resumed, and a polysomnography evaluation at term (40 weeks 6 days gestational age) was obtained due to the persistent nature of desaturations. The study was notable for 77 central hypopnea events per hour (Apnea-Hypopnea Index 79/h; normal for age is 15/h) and periodic breathing occupying approximately

50% of total sleep time (normal for age is 5%). The average desaturation index was 34/h and the lowest SpO_2 was 81%, though results were confounded by supplemental oxygen titration throughout the entirety of the study, helping to artificially maintain saturations greater than 90%. With the severity of the polysomnography results during 7.5 hours of overnight sleep, the infant was swiftly intubated and mechanically ventilated (SIMV pressure control, pressure support mode) as additional physiologic testing in keeping with the American Thoracic Society Statement on Congenital Central Hypoventilation Syndrome (CCHS) was completed.

At the onset of this evaluation and in discussions with the Molecular Diagnostics Laboratory about the patient's phenotype, preliminary analysis of the suggested microarray detected a heterozygous 369 kilobyte deletion on Chromosome 4p13 that included the full *PHOX2B* gene (4p12) and one neighboring gene on one allele. Consequently, the infant was evaluated for congenital neural crest tumors by chest radiograph evaluating along the sympathetic chain and abdominal/pelvis ultrasonography to evaluate for adrenal tumors, as well as urine catecholamines (to identify a neuroblastoma). Furthermore, 72-hour Holter recording to identify prolonged cardiac sinoatrial pauses was performed but with longest R-R interval 1.0 seconds. Because of the nature of the infant's *PHOX2B* mutation and recognition of an autosomal dominant inheritance pattern to CCHS and *PHOX2B* mutations, the proband's parents were tested with the Multiplex Ligation-dependent Probe Amplification (MLPA) dependent Probe Amplification (MLPA) *PHOX2B* test. It was determined the whole gene *PHOX2B* deletion was paternally inherited; linearly related relatives of the father and the proband are undergoing genetic testing to identify the generation source of the unique *PHOX2B* mutation with overt variable phenotype penetrance.

Discussion

Diagnostics

The paired-like homeobox gene 2B (*PHOX2B*), located on chromosome 4p, at 4p12, is the disease-defining gene for CCHS [1, 2]. CCHS-related *PHOX2B* mutations are heterozygous and diagnosis is confirmed by stepwise (also termed sequential) *PHOX2B* genetic testing (initially, the screening test, then if negative, sequencing test, and lastly if the prior tests are negative, deletion/duplication MLPA test). The *PHOX2B* allele has 20 alanines in exon 3 (normal genotype 20/20 indicating the number of alanines on each allele). This *PHOX2B* homeobox gene encodes a highly conserved transcription factor that determines neuron cell fate among sympathetic, parasympathetic, and enteric neurons of the autonomic nervous system. Additionally, *PHOX2B* has a key role in control of breathing by contributing to the formation of the retrotrapezoid nucleus which lies on the rostral surface of the medulla and contributes to central chemosensitivity [3].

A *PHOX2B* mutation is inherited in an autosomal-dominant fashion through germinal mutation or germline mosaicism (collectively 5–35% of infants) or as a *de*

novo mutation. Genetic testing for the most common *PHOX2B* genotypes is clinically available as a screening test and detects all polyalanine repeat expansion mutations (PARMs) (genotypes 20/24–20/33) (accounting for 90–92% of the CCHS cases) and large non-PARM (NPARM) deletions (primarily 35 and 38 base pair deletions), affecting the 20 alanine repeat regions of exon 3. Additionally, the screening test is the only clinically available test that will identify low level somatic mosaicism in the subset of parents who are affected. If the *PHOX2B* screening test is negative but the phenotype is convincing for CCHS, *PHOX2B* sequencing analysis is performed to identify smaller NPARMs (missense, nonsense, frameshift, or stop codon mutations); NPARMs will collectively account for 8–10% of CCHS cases. If the *PHOX2B* screening and sequencing tests are negative, deletion/duplication testing with MLPA is the next step to identify loss of the *PHOX2B* gene as well as potentially neighboring genes [4]. This was the case for the infant described above, he is heterozygous for a mutation involving the entire *PHOX2B* gene and a neighboring gene on one allele.

With clinical suspicion for the CCHS phenotype, genetic testing is used to confirm *PHOX2B*-CCHS-specific mutations. Since 1970, over 100 CCHS-causing *PHOX2B* mutations have been identified with ~2,000 cases confirmed and an estimated incidence of 1/200,000 live births; thus, CCHS is grossly underdiagnosed [3]. With established pediatric diagnoses, parental testing of children with CCHS is recommended to determine if mosaicism exists in either parent. Identification is essential for family planning and to address potential health risks of mosaic parents. In the presented case, the sibling and extended family members were then tested with the *PHOX2B* deletion/duplication MLPA test. Preimplantation genetics is a consideration for CCHS probands as well as mosaic parents. For pregnancies in which the fetus is known to have a *PHOX2B* mutation, and termination of the pregnancy is not a consideration, the infant can be delivered in a quaternary care medical center to ensure a smooth perinatal transition.

Phenotype

CCHS-related facial features include a boxy-shaped face, with a flattened profile and an overturned lateral one-third of the upper lip vermillion border such that it is flesh colored instead of pink, with the facies most easily identifiable among the more common heterozygous *PHOX2B* PARMs (Fig. 17.1) [4]. Children with the NPARMs additionally may have epicanthal folds and reduced movement of the lower one-third of the face. Strabismus, anisocoria, and altered pupillary responses to light stimulus are relatively common in CCHS.

Clinically, the hallmark feature of CCHS is central hypoventilation with markedly attenuated peripheral and central chemoreceptor responsiveness awake and asleep. Patients often have inappropriately elevated respiratory rates through infancy and persistently monotonous respiratory rates with diminutive tidal volumes and occasionally apnea. Children with severe CCHS phenotypes will demonstrate profound hypoventilation during quiet and exertional activity awake as well as during

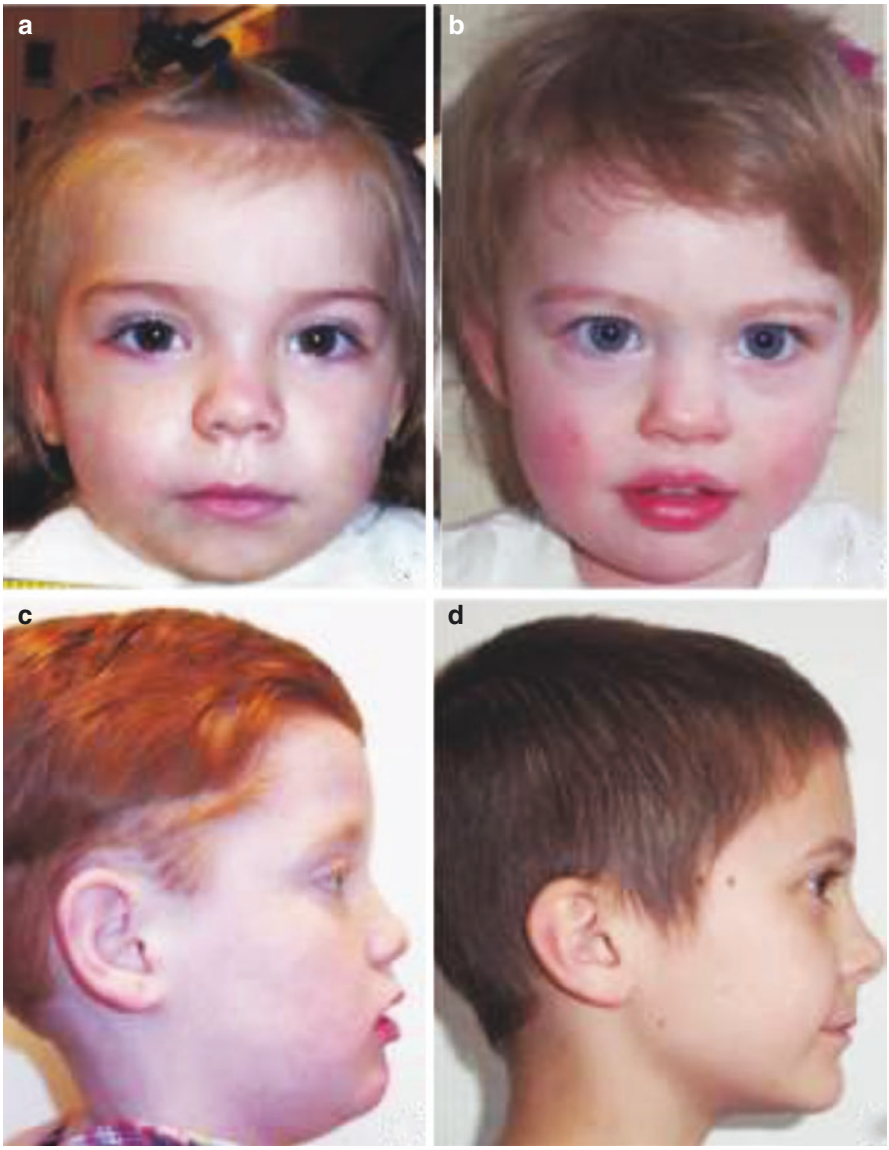


Fig. 17.1 Photographs of children with CCHS (**a** (20/25 genotype) and **c** (20/27)) and control subjects (**b**,**d**) matched for age, gender, and ethnicity. Children with CCHS have characteristic facial features including a boxy-shaped face that is shorter and flatter than matched controls, and the "lip trait" consisting of inflection of the lateral 1/3 of the upper vermillion border so it is flesh-colored instead of pink. (Reproduced with permission, Todd et al. 2006)

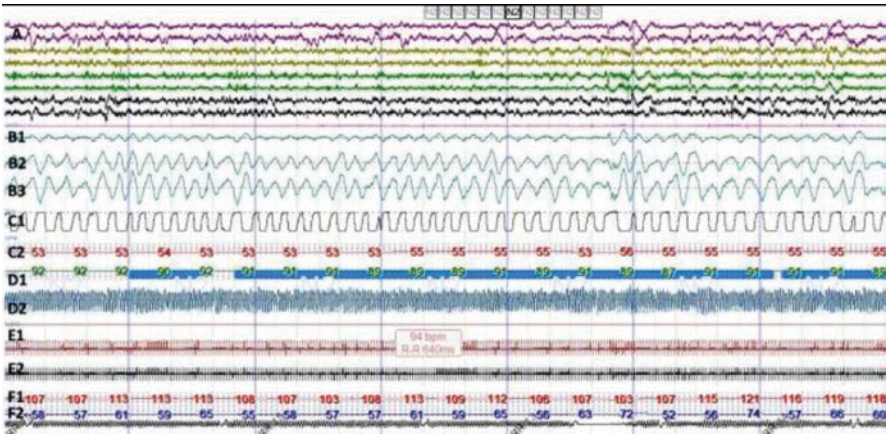


Fig. 17.2 Polysomnogram of patient with CCHS (20/27 genotype) during non-REM sleep and transiently without respiratory support to perform an intra-sleep spontaneous breathing trial. The montage in descending order consists of EEG and EOG tracings (A), respiratory inductance plethysmography bands (RIP; thoracic, abdominal, summation) (B1,B2,B3), end-tidal carbon dioxide waveforms and values (mmHg) (C1,C2), peripheral pulse oximeter value (%) and waveform (D1,D2), electrocardiogram (E1,E2), and finger probe blood pressure (systolic F1, diastolic F2) with the beat-to-beat waveform. Each epoch consists of 30 seconds denoted by the thickened vertical lines. The child demonstrated a central hypopnea without overt change in depth or rate of breathing despite the related hypercarbia and subsequent desaturations. Note the thoracic RIP band amplitude is diminished, while the continuous end-tidal carbon dioxide waveform shows regular breaths, without overt paradoxical inward movement of the chest on inspiration

sleep, though minute ventilation during rapid eye movement (REM) sleep tends to be "more normal" than in non-REM sleep primarily due to added spontaneous breaths. As in this infant, patients with CCHS typically have severely diminished chemoreceptor sensitivity and lack corrective efforts for normal gas exchange such as maintaining a regular respiratory rate and adjusting tidal volumes in the event of hypercarbia and hypoxemia (Fig. 17.2). Patients with CCHS consistently lack overt behavioral and perceived responses to hypercarbia and hypoxia such as dyspnea, complaint of headache, or sense of anxiety despite the physiologic challenges during awake activities of daily living. Additionally, children with CCHS do not awaken in response to hypercarbia and hypoxemia [5].

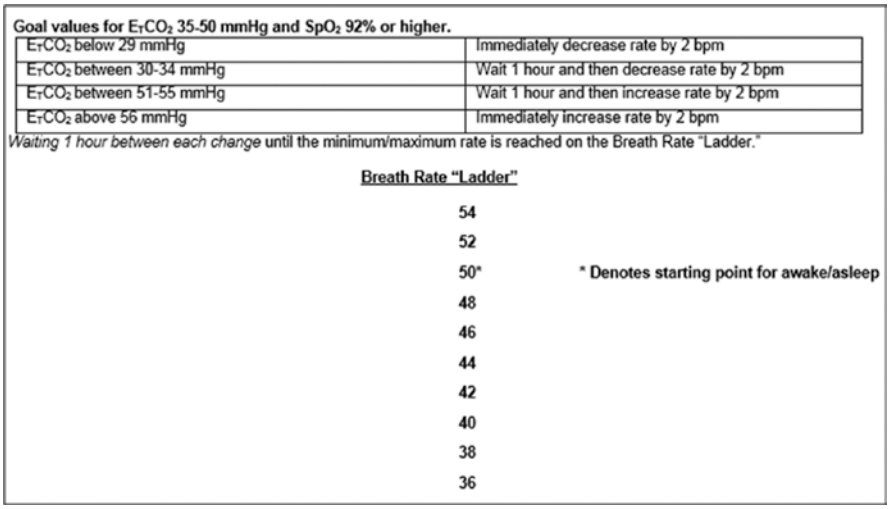
Further comorbidities of CCHS include Hirschsprung disease, esophageal and gastrointestinal dysmotility, and in the first year of life feeding intolerance as exemplified in the presented case. Patients with CCHS often demonstrate reduced HR variability, possibly due to a decrease in baroreflex sensitivity and sympathetic input, and prolonged cardiac sinoatrial pauses can occur. Children with CCHS are also at risk for neural crest tumors, most commonly neuroblastomas, ganglioneuromas, and ganglioneuroblastomas, although prevalence and type of tumor varies by *PHOX2B* genotype (neuroblastoma occurs in ~50% of children with NPARMs and ganglioneuroma and ganglioneuroblastoma occur in less than 5% of children with the longer PARMs (reports in 20/29, 20/30 and 20/33 genotypes). Patients with CCHS have reduced core and peripheral temperatures with attenuated circadian

variation, dampened temperature response to infection with rare febrile response, and elevated pain threshold [1]. Autopsy of two neonates with CCHS (one with a *PHOX2B* PARM (20/27) and one with an NPARM mutation (8 base pair deletion/frameshift)) revealed loss of noradrenergic nerve fibers in the cerebral nucleus locus coeruleus, thought to be associated with sympathetic activation. A murine model reproduced this finding in early onset *PHOX2B* NPARM mutations (8 base pair deletion; at less than 10.5 days embryologically) revealing a loss of functional locus coeruleus, abnormal adrenergic neurons, and absence of the retrotrapezoid nucleus, associated with chemoreceptor insensitivity [6].

Treatment and Surveillance

CCHS disease severity and morbidity varies by genetic mutation among the most common *PHOX2B* mutations. PARMs and NPARMs are well-described, while whole *PHOX2B* deletions resulting in potential haploinsufficiency (such as the case study above) and mosaicism have less defined phenotypes due in large part to their reduced incidence. In general, the longer PARM expansions, especially 20/27 and longer, and NPARMS have more severe phenotypes [7].

CCHS is typically diagnosed in the newborn period except for a subset of cases diagnosed after one month of age and sometimes not until adulthood (later-onset CCHS, LO-CCHS). Since the *PHOX2B* genetic mutation informs regarding the CCHS phenotype, it is essential to identify the specific mutation to allow for anticipatory management. CCHS is a life-long condition *without* expectation to "wean" a child from life support. After diagnosis and at hospital discharge to home, infants should have a portable mechanical ventilator and a back-up portable ventilator, a tracheostomy to provide a secure airway ideally with a tight-to-the-shaft cuffed tracheostomy tube (to minimize air leak asleep but allow for voice awake), a pulse oximeter that shows waveform and saturation value, a capnography monitor that shows the exhaled carbon dioxide waveform and actual value, and an experienced registered nurse with expertise in caring for an infant/child who is ventilator-dependent with a control of breathing deficit (as the child with CCHS will not show typical indicators of illness). The ATS Statement on CCHS advocates for diligent at-home monitoring with pulse oximeter and end tidal. Ideally, nursing should provide continuous one-on-one care when the infant or child is awake and asleep, attending to the continuously used monitors, making ventilator changes as needed accordingly, and providing immediate intervention in acute situations to sustain life support [8]. Use of custom ventilator management with clear guidelines for the parents and home care providers to adjust respiratory support according to monitor values at home (called the custom "ventilator ladder") has reduced need for hospitalization. For example, patients on mechanical ventilation via tracheostomy have varied gas exchange between different levels of activity and while awake or during sleep. Nursing or family members can respond to elevated carbon dioxide levels by following a prescribed "ladder" ventilator plan and increasing the respiratory rate. The case's respiratory plan and ventilator ladder are displayed in Fig. 17.3.



Goal values for E_TCO_2 35-50 mmHg and SpO_2 92% or higher.

E_TCO_2 below 29 mmHg	Immediately decrease rate by 2 bpm
E_TCO_2 between 30-34 mmHg	Wait 1 hour and then decrease rate by 2 bpm
E_TCO_2 between 51-55 mmHg	Wait 1 hour and then increase rate by 2 bpm
E_TCO_2 above 56 mmHg	Immediately increase rate by 2 bpm

Waiting 1 hour between each change until the minimum/maximum rate is reached on the Breath Rate "Ladder."

Breath Rate "Ladder"

54
52
50* * Denotes starting point for awake/asleep
48
46
44
42
40
38
36

Fig. 17.3 Example of custom mechanical "ventilator ladder" prescription for patient with CCHS described in case. The ladder provides guidance for parents, home nursing, and care providers to adjust ventilator settings in varied conditions (asleep, awake in varied levels of exertion) according to the child's continuously monitored end-tidal capnography values. E_TCO_2 end-tidal carbon dioxide, mmHg millimeters of mercury, bpm breaths per minute

Independent of genotype, the ATS recommends positive pressure ventilation through a tracheostomy for the first several years of life to ensure optimal gas exchange for well-being, growth, and development [8]. Neurocognitive outcome in patients with CCHS is variable, with mean full scale IQ scores one standard deviation below the norm (mean score is 100 and standard deviation is 15 points) [9]. It is not clear if this variation and reduced mean scores are intrinsic to CCHS, due to alteration in cerebrovascular autoregulation, or due to recurrent physiologic compromise, even with conservative management [10]. Therefore, in infancy and early childhood, physiologic evaluation awake and asleep should be performed at a minimum every six months in varied activities of daily living, in a controlled testing environment. This is particularly important with advancing age, growth, milestone achievements, and changes in activity levels and metabolic demands with varying gas exchange. Furthermore, these comprehensive in-laboratory/in-hospital evaluations are paramount as children with CCHS do not demonstrate behavioral changes to being under-supported with resultant hypoxemia or hypercarbia. Hence, comprehensive evaluations monitoring patient's autonomic functions and gas exchange with various activities awake and asleep are necessary to provide guidance with aim to offer the highest quality of life within the patient's physiologic capacity.

For the child with CCHS who is ventilator-dependent awake and asleep, phrenic nerve-diaphragm pacers are a consideration to allow for awake time mobility and improved quality of life [11]. For the child who requires respiratory support during sleep only, nasal or full face mask non-invasive ventilation might be a consideration,

although not until the child can take responsibility for replacing the mask such as after using the bathroom during the night and not until the child's facial features are adequately developed to prevent further facial flattening beyond the innate configuration of the CCHS face. Method of daytime and nighttime support varies by genotype and disease severity, patient age, airway structural maturity and integrity, the availability and quality of home health care, insurance coverage, the patient and family goals of care, and other factors. Most patients with short PARM mutations (20/24 and 20/25) have milder hypoventilation and require only nighttime support. With rare exceptions, patients with longer PARM and NPARM mutations require 24-h per day artificial respiratory support.

The aforementioned morbidities will need to be monitored as well. Semi-annually under 3 years of age and annually thereafter, a 72-h Holter monitoring to screen for cardiac sinoatrial pauses is recommended as the prevalence of 3 s or longer pauses is above 80% of patients with the 20/27 *PHOX2B* genotype. For patients with cardiac pauses ≥3 s, a bipolar cardiac pacemaker is typically recommended. Evaluation for neural crest tumors in patients with longer PARM mutations (20/28–20/33) is recommended every 6 months until age 3 years, then annually thereafter, including chest anteroposterior and lateral radiographs and abdominal/pelvic ultrasound to identify neural crest tumors (primarily ganglioneuroma and ganglioneuroblastoma). For patients with NPARMs, a chest X-ray and abdominal and pelvic ultrasound, potentially with urine catecholamines, should be performed initially every 3 months until age 3 years, and then every 6 months until at least age 7 (primarily evaluating for a neuroblastoma). Lastly, if the newborn has abdominal distension and failure to pass stool, consider biopsy for rectal ganglion nerve cells to evaluate for Hirschsprung disease with the risk of 20–30% occurrence in PARMs (20/26–20/33) and 50% or higher occurrence in patients with NPARMs [8].

Clinical Pearls

- Congenital central hypoventilation syndrome (CCHS) is caused by a mutation in the highly conserved *PHOX2B* gene, a gene essential to the embryologic development of the autonomic nervous system and intact control of breathing.
- CCHS-related *PHOX2B* mutations are heterozygous and include polyalanine repeat expansion mutations (PARMs) (90–92% of cases), non-PARMs (NPARMs) (8–10% of cases), and whole gene deletions (less than 1% of cases).
- The *PHOX2B* gene mutation and genotype allows for anticipatory management relative to disease severity and prevalence of morbidities.
- A principal feature of CCHS is diminished to absent central and peripheral chemoreceptor responsiveness awake and asleep, even in the children who seem to have adequate awake spontaneous breathing.

- On polysomnography, the patient with CCHS will demonstrate diminutive tidal volumes, monotonous respiratory rates (mildly elevated to normal for age), hypercarbia and hypoxemia without a physiologic or arousal response, and heart rate that is often elevated for age and with limited variability.
- Additional features of CCHS include cardiac sinoatrial pauses, Hirschsprung disease, esophageal and gastrointestinal dysmotility, and altered pupillary response to light. Although occurrence is rare overall, screening for neural crest tumors is imperative in children with longer PARMs and essential in patients with NPARMs in whom the tumor risk is close to 50%.
- For the first several years of life, the standard of care is continuous mechanical ventilation for 24 h a day via tracheostomy, except for the most mildly affected that will only require support asleep. Phrenic nerve diaphragm pacing for use during wakefulness in children who require continuous mechanical ventilation via tracheostomy is an effective means to improve quality of life.
- Patients are followed every 6 months until age 3 years and then annually thereafter with comprehensive in-hospital physiologic testing to ensure adequate oxygenation and ventilation during awake activities of daily living and sleep with adjustment of respiratory support as needed and to screen for anticipated comorbidities, with the ultimate goal of optimizing neurodevelopmental outcomes and quality of life.

References

1. Amiel J, Laudier B, Attie-Bitach T, et al. Polyalanine expansion and frameshift mutations of the paired-like homeobox gene PHOX2B in congenital central hypoventilation syndrome. Nat Genet 2003;33:459–61.
2. Weese-Mayer DE, Berry-Kravis EM, Zhou L, et al. Idiopathic congenital central hypoventilation syndrome: analysis of genes pertinent to early autonomic nervous system embryologic development and identification of mutations in PHOX2b. American journal of medical genetics Part A 2003;123A:267–78.
3. Weese-Mayer DE, Rand CM, Zhou A, Carroll MS, Hunt CE. Congenital central hypoventilation syndrome: a bedside-to-bench success story for advancing early diagnosis and treatment and improved survival and quality of life. Pediatric research 2017;81:192.
4. Jennings LJ, Yu M, Zhou L, Rand CM, Berry-Kravis EM, Weese-Mayer DE. Comparison of PHOX2B testing methods in the diagnosis of congenital central hypoventilation syndrome and mosaic carriers. Diagnostic Molecular Pathology: The American Journal Of Surgical Pathology, Part B 2010;19:224.
5. Todd ES, Weinberg SE, Berry-Kravis EM, et al. Facial Phenotype in Children and Young Adults with PHOX2B-Determined Congenital Central Hypoventilation Syndrome: Quantitative Pattern of Dysmorphology. Pediatric research 2006;59:39.

6. Nobuta H, Cilio M, Danhaive O, et al. Dysregulation Of Locus Coeruleus Development In Congenital Central Hypoventilation Syndrome. American Journal Of Respiratory And Critical Care Medicine 2015;191.
7. Weese-Mayer DE, Berry-Kravis EM, Ceccherini I, et al. An official ATS clinical policy statement: Congenital central hypoventilation syndrome: genetic basis, diagnosis, and management. American journal of respiratory and critical care medicine 2010;181:626–44.
8. Zelko FA, Stewart TM, Brogadir CD, Rand CM, Weese-Mayer DE. Congenital central hypoventilation syndrome: Broader cognitive deficits revealed by parent controls. Pediatric pulmonology 2018;53:492–7.
9. Carroll MS, Patwari PP, Kenny AS, Brogadir CD, Stewart TM, Weese-Mayer DE. Residual chemosensitivity to ventilatory challenges in genotyped congenital central hypoventilation syndrome. Journal Of Applied Physiology (Bethesda, Md : 1985) 2014;116:439.
10. Valika T, Chin AC, Thompson DM, et al. Airway Obstruction during Sleep due to Diaphragm Pacing Precludes Decannulation in Young Children with CCHS. Respiration; international review of thoracic diseases 2019;98:263–7.

Chapter 18
Sleep Disordered Breathing and Prader-Willi Syndrome

Caroline U. A. Okorie and David G. Ingram

Case Presentation

A 12-year-old male child presents to a sleep clinic for concern for sleep apnea. The parents report a several-years history of habitual loud snoring, witnessed apneas, daytime sleepiness, and restless sleep. Prenatal history is significant for polyhydramnios and breech position. As an infant, the child was noted to have low tone, poor suck, and feeding difficulties. As a toddler and young child, parents noticed that his appetite increased substantially, and he became obese but with short stature. He is currently in the 7th grade but is developmentally delayed and has an individualized education plan. Overnight polysomnography (PSG) demonstrated an obstructive apnea-hypopnea index (AHI) of 12/h, normal oxygen saturation and carbon dioxide gas exchange, and sleep architecture remarkable for rapid eye movement (REM) sleep onset latency of 10 min and overall generally fragmented sleep. The tonsils were minimal so the child was treated with continuous positive airway pressure (CPAP). CPAP download after 3 months of use demonstrated excellent compliance (30/30 days, average use of 8.5 h per night) and efficacy (residual AHI 0.4/h and parent report resolution of snoring with CPAP use). However, the patient continued to fall asleep frequently during the day. Subsequent PSG (on CPAP) followed by Multiple Sleep Latency Test (MSLT) the next day demonstrated a mean sleep latency of 5 min and three out of five sleep onset REM episodes (SOREMs). The child was diagnosed with type 2 narcolepsy and responded well to modafinil.

C. U. A. Okorie (✉)
Lucile Packard Children's Hospital, Stanford University School of Medicine, Department of Pediatrics, Division of Pulmonary, Asthma and Sleep, Palo Alto, CA, USA
e-mail: cokorie@stanford.edu

D. G. Ingram
Children's Mercy Hospital, Kansas City, MO, USA

C. Won (ed.), *Complex Sleep Breathing Disorders*,
https://doi.org/10.1007/978-3-030-57942-5_18

Discussion

Prader-Willi syndrome (PWS) is a complex genetic disorder that results from a loss of function of paternally expressed genes from the chromosome 15q11.2–q13. It occurs secondary to paternal chromosomal deletion in 70–75% of cases or with maternal disomy in 20–25% of cases and abnormal methylation of the chromosome in 2–5% of cases. PWS occurs in 1 in 10,000–25,000 live births [1, 2].

The diagnostic criteria for PWS, first published in 1993, included an extensive list of major and minor criteria. They include a list of clinical symptoms (e.g., hypotonia, feeding difficulties that evolve into hyperphagia, hypogonadism, developmental delay) and examination findings (e.g., characteristic facial features: dolichocephaly, narrow face, almond-shaped eyes, small mouth, thin upper lip, down-turning corners of mouth) [3]. Patients with PWS have a characteristic age-dependent clinical presentation, starting with hypotonia and poor feeding from birth to 2 years of age. As the child becomes older, global developmental delay becomes more apparent, and school-aged children exhibit a characteristic hyperphagia and preoccupation with food. Hypothalamic hypogonadism and behavior problems (e.g., compulsive behaviors, temper tantrums) are more pronounced by the early teenage years. Despite characteristic clinical features, a retrospective review of patients with PWS demonstrated that 16.7% of patients with a molecular diagnosis of PWS did not meet the extensive clinical criteria laid out in 1993, suggesting the published criteria was too exclusive [4]. In the age of readily available genetic testing, a new approach to the diagnosis of PWS has been recommended wherein the focus is on determining clinical features sufficient to prompt DNA testing [4]. This lower threshold for genetic testing has allowed earlier detection and treatment of PWS. Gunay-Aygun et al. suggested the following children undergo DNA testing for PWS: (A) children younger than 2 years old with hypotonia and poor suck; (B) children ages 2–6 years with current or past hypotonia, history of poor suck, and global developmental delay; (C) children ages 6–12 years with current or past hypotonia, global developmental delay, and hyperphagia or obsession with food; and (D) children 13 years or older with current or past hypotonia, cognitive impairment, hyperphagia, hypothalamic hypogonadism, and/or behavioral problems (e.g., tantrums, compulsive tendencies) [4].

Ventilatory Control

The ventilatory responses to hypoxemia and hypoventilation are altered in patients with PWS [5, 6]. Normally, in response to hypoxia, peripheral chemoreceptors (in the carotid bodies) send a signal to increase the tidal volume or respiratory rate. Some PWS individuals demonstrate an absent or blunted hypoxic ventilatory response (HPVR), and a portion of patients have a paradoxical reaction to hyperoxia (showing increased minute ventilation) or a paradoxical reaction to hypoxia

(decreased minute ventilation). In addition, an absent or blunted hypercapnic ventilatory response (HCVR) is seen in patients with PWS. Again, in normal individuals, the peripheral chemoreceptors detect a rise in arterial pressure of carbon dioxide ($PaCO_2$) and will stimulate increased minute ventilation in an effort to increase oxygen levels and to decrease carbon dioxide (CO_2) levels.

Abnormal chemo-responsiveness is also evident in PWS during non-rapid eye movement (NREM) sleep. For example, respiratory rate during sleep does not increase in response to hypoxia or hypercapnia. Likewise, arousal and cardiac responses to hypoxia are abnormal. When subjects were exposed experimentally to hypoxic challenge, PWS subjects were less likely than age- and BMI-matched controls to have an arousal or mount a tachycardia response [7]. It is unclear whether the injury lies in dysfunctional peripheral chemoreceptors, defective afferent neuronal pathways, or defective central or efferent mechanisms.

Obstructive Sleep Apnea

The prevalence of obstructive sleep apnea (OSA) in patients with PWS is very high, estimated to be around 80%, compared to 2–3% of the general pediatric population [2]. About half of cases are mild (AHI 1–5 events/h), while about a quarter have moderate OSA (AHI 5–10/h), and the remaining quarter have severe OSA (AHI > 10/h). In this population, OSA appears to affect girls and boys equally. OSA is caused by a combination of factors, including craniofacial anatomy (such as a narrow upper airway and micrognathia), low tone of the upper airway, and weak respiratory muscles due to generalized hypotonia. The high prevalence of obesity among the PWS population also adds to the increased risk for OSA in this population [8–10]. Adenotonsillectomy can be an effective first-line option for treatment in PWS children with enlarged adenoids and tonsils. However, many will also have residual OSA despite adenotonsillectomy due to other contributing factors such as upper airway hypotonia. For this reason, a post-surgery study is generally recommended in this population. Residual OSA will require further management including with continuous positive airway pressure or non-invasive ventilation therapy.

Growth Hormone

Growth hormone (GH) was approved by the FDA for treatment of patients with PWS in 2000. The exact mechanism of growth hormone benefit is unclear; however, it is known to increase linear growth, increase lean body mass, and decrease total body fat [11]. Growth hormone treatment in children with PWS is associated with improved cognitive performance and daily living skills [12]. It is even associated with an improved ventilatory response to hypercapnia [13].

Exogenous growth hormone may increase serum insulin-like growth factor 1, or IGF-1, which in turn may stimulate growth of lymphoid tissues. Increased lymphoid tissue may lead to increased adenoid/tonsillar hypertrophy and increased upper airway resistance, leading to potential worsening of OSA and, in the most severe cases, respiratory distress or death. This potential risk was highlighted by a review of death reports of 64 children with PWS, the majority of whom died within 9 months of starting GH treatment, with the most common cause of death being respiratory insufficiency [14]. Furthermore, some children with PWS and known sleep disordered breathing at baseline have been shown to experience a worsening of OSA severity necessitating discontinuation of GH; that said, the majority of children did not develop OSA, even when followed for 2 years [15]. On the other hand, as discussed above, GH treatment improves respiratory muscle strength and ventilatory response to hypercapnia. Therefore, whether or not GH truly increases risk of worsening OSA in children with PWS remains an unresolved issue, and many advocate for evaluation for sleep disordered breathing prior to starting GH therapy until more definitive evidence is available [16]. Currently, the Consensus Guidelines for Recombinant Human Growth Hormone Therapy in Prader-Willi Syndrome suggest patient and parent counseling about the potential association between GH and death prior to initiating therapy. They also recommend a sleep study and treatment of any underlying sleep disordered breathing prior to GH initiation. It is recommended that GH be started at a low dose while monitoring IGF-1 levels. The American Academy of Pediatrics recommends polysomnography 6–10 weeks after starting GH in children with PWS [17]. The Growth Hormone Research Society recommends a sleep study within the first 3–6 months, while others recommend annual testing [18].

Central Sleep Apnea

Central sleep apnea (CSA) is also seen in patients with PWS, mainly in patients less than 2 years of age, and predominantly during REM sleep. This is thought to be related to immature ventilatory control centers and a higher arousal threshold to hypercapnia and the blunted HCVR and HPVR, as discussed above. In other words, the central apneas that develop during REM in PWS are of the hypoventilatory, hypercapnic phenotype (as opposed to the normo-/hypocapnic, high loop gain, NREM-predominant phenotype). Central apneas are very commonly seen in infants with PWS. Interestingly, supplemental oxygen has shown to be effective in reducing central apneas [19, 20]. Supplemental oxygen is thought to generally worsen hypercapnic CSA by further blunting respiratory responses to hypercapnia. However, in PWS, despite being largely a hypoventilatory, hypercapnic CSA phenotype due to blunted HCVR and HPVR, supplemental oxygen in the few studies performed has shown decrease in central AHI. As infants grow and respiratory centers mature, central apneas may eventually decrease in severity or completely resolve.

Sleep-Related Hypoventilation

Sleep-related hypoventilation may also occur in PWS due to a high propensity for obesity, hypotonia, respiratory muscle weakness, and kyphoscoliosis. The level of hypotonia is generally not severe enough to cause chronic respiratory failure in these patients. However, when comorbid with severe obesity and kyphoscoliosis, for example, significant sleep-related hypoventilation may result, particularly during REM sleep. Sleep-related hypoventilation in PWS may be associated with dramatic oxygen desaturations due to a low arousal threshold and low HCVR and HPVR. These patients may do best with non-invasive or invasive home ventilators.

Hypersomnia

The majority of patients with PWS have excessive daytime sleepiness [21]. At first glance, this may be attributed to sleep disordered breathing. However, there are many patients with PWS who continue to have excessive daytime sleepiness despite adequate treatment of OSA and assurance of adequate quantity and quality of sleep [1, 22]. The etiology of persistent excessive daytime sleepiness is thought to be multifactorial with general hypothalamic dysfunction (including adrenal hypothyroidism and defects in adrenal response). Patients with PWS also have poor adrenal response in times of stress [23].

Excessive daytime sleepiness may also be related to narcolepsy-like phenotype in which hypersomnia persists despite good quality and quantity of sleep. A subset of these patients even have cataplexy and show decreased levels of hypocretin-1/orexin-A in the cerebral spinal fluid [1, 24]. Central nervous system stimulants, like modafinil, have shown to benefit PWS patients suffering persistent hypersomnia despite treatment of sleep disordered breathing [25].

Clinical Pearls

- There should be a low threshold for genetic testing in patients with clinical symptoms suggestive of PWS.
- Patients with PWS have a high risk of sleep disordered breathing and should undergo polysomnography to objectively assess for obstructive sleep apnea, central sleep apnea, and/or hypoventilation. These sleep-related breathing disorders are related to patient's hypotonia, small upper airways, obesity, impaired pulmonary function, and impaired hypercapnic/hypoxemic ventilatory responses.

- Growth hormone is an effective treatment for young children with PWS and can increase muscle tone, increase lean body mass, reduce body fat, and improve lung function. Of note, there are concerns regarding incidences of sudden death shortly after starting growth hormone therapy. The Food and Drug Administration (FDA) issued a warning in 2003 about a potential association between growth hormone therapy and death particularly in PWS children with severe obesity, history of respiratory impairment or sleep apnea, or an unidentified respiratory infection.
- The Consensus Guidelines for Recombinant Human Growth Hormone Therapy in Prader-Willi syndrome suggest counseling and polysomnography pre- and post-treatment with growth hormone.
- Hypersomnia can be seen out of proportion to sleep disordered breathing and may be related to hypocretin/orexin deficiency in PWS. The patients may also exhibit cataplectic symptoms. Stimulants may be highly effective for treating central hypersomnia.

References

1. Gillett ES, Perez IA. Disorders of sleep and ventilatory control in Prader-Willi syndrome. Diseases. 2016. https://doi.org/10.3390/diseases4030023.
2. Sedky K, Bennett DS, Pumariega A. Prader Willi syndrome and obstructive sleep apnea: co-occurrence in the pediatric population. J Clin Sleep Med. 2014;10:403–9.
3. Holm VA, Cassidy SB, Butler MG, Hanchett JM, Greenswag LR, Whitman BY, Greenberg F. Prader-Willi syndrome: consensus diagnostic criteria. Pediatrics. 1993;91:398–402.
4. Gunay-Aygun M, Schwartz S, Heeger S, O'Riordan MA, Cassidy SB. The changing purpose of Prader-Willi syndrome clinical diagnostic criteria and proposed revised criteria. Pediatrics. 2001;108:E92.
5. Menendez AA. Abnormal ventilatory responses in patients with Prader-Willi syndrome. Eur J Pediatr. 1999;158:941–2.
6. Gozal D, Arens R, Omlin KJ, Ward SL, Keens TG. Absent peripheral chemosensitivity in Prader-Willi syndrome. J Appl Physiol. 1994;77:2231–6.
7. R. Arens, D. Gozal, K. J. Omlin, F. R. Livingston, J. Liu, T. G. Keens, S. L. Ward, (1994) Hypoxic and hypercapnic ventilatory responses in Prader-Willi syndrome. Journal of Applied Physiology 77(5):2224–30.
8. Khan MJ, Gerasimidis K, Edwards CA, Shaikh MG. Mechanisms of obesity in Prader-Willi syndrome. Pediatr Obes. 2018;13:3–13.
9. Salehi P, Leavitt A, Beck AE, Chen ML, Roth CL. Obesity management in Prader-Willi syndrome. Pediatr Endocrinol Rev. 2015;12:297–307.
10. Robinson-Shelton A, Malow BA. sleep disturbances in neurodevelopmental disorders. Curr Psychiatry Rep. 2016;18:6.
11. Bakker NE, Lindberg A, Heissler J, Wollmann HA, Camacho-Hübner C, Hokken-Koelega AC, KIGS Steering Committee. Growth hormone treatment in children with Prader-Willi syndrome: three years of longitudinal data in prepubertal children and adult height data from the KIGS database. J Clin Endocrinol Metab. 2017;102:1702–11.
12. Dykens EM, Roof E, Hunt-Hawkins H. Cognitive and adaptive advantages of growth hormone treatment in children with Prader-Willi syndrome. J Child Psychol Psychiatry. 2017;58:64–74.

13. Katz-Salamon M, Lindgren AC, Cohen G. The effect of growth hormone on sleep-related cardio-respiratory control in Prader-Willi syndrome. Acta Paediatr. 2012;101:643–8.
14. Tauber M, Diene G, Molinas C, Hébert M. Review of 64 cases of death in children with Prader-Willi syndrome (PWS). Am J Med Genet A. 2008;146A:881–7.
15. Al-Saleh S, Al-Naimi A, Hamilton J, Zweerink A, Iaboni A, Narang I. Longitudinal evaluation of sleep-disordered breathing in children with Prader-Willi syndrome during 2 years of growth hormone therapy. J Pediatr. 2013;162:263–8.e1.
16. Wolfgram PM, Carrel AL, Allen DB. Long-term effects of recombinant human growth hormone therapy in children with Prader-Willi syndrome. Curr Opin Pediatr. 2013;25:509–14.
17. McCandless SE, Committee on Genetics. Clinical report—health supervision for children with Prader-Willi syndrome. Pediatrics. 2011;127:195–204.
18. Deal CL, Tony M, Höybye C, Allen DB, Tauber M, Christiansen JS, 2011 Growth Hormone in Prader-Willi Syndrome Clinical Care Guidelines Workshop Participants. Growth Hormone Research Society workshop summary: consensus guidelines for recombinant human growth hormone therapy in Prader-Willi syndrome. J Clin Endocrinol Metab. 2013;98:E1072–87.
19. Urquhart DS, Gulliver T, Williams G, Harris MA, Nyunt O, Suresh S. Central sleep-disordered breathing and the effects of oxygen therapy in infants with Prader-Willi syndrome. Arch Dis Child. 2013;98:592–5.
20. Tan H-L, Urquhart DS. Respiratory complications in children with Prader Willi syndrome. Paediatr Respir Rev. 2017;22:52–9.
21. Ghergan A, Coupaye M, Leu-Semenescu S, Attali V, Oppert J-M, Arnulf I, Poitou C, Redolfi S. Prevalence and phenotype of sleep disorders in 60 adults with Prader–Willi syndrome. Sleep. 2017. https://doi.org/10.1093/sleep/zsx162.
22. Manni R, Politini L, Nobili L, Ferrillo F, Livieri C, Veneselli E, Biancheri R, Martinetti M, Tartara A. Hypersomnia in the Prader Willi syndrome: clinical-electrophysiological features and underlying factors. Clin Neurophysiol. 2001;112:800–5.
23. Camfferman D, McEvoy RD, O'Donoghue F, Lushington K. Prader Willi syndrome and excessive daytime sleepiness. Sleep Med Rev. 2008;12:65–75.
24. Omokawa M, Ayabe T, Nagai T, Imanishi A, Omokawa A, Nishino S, Sagawa Y, Shimizu T, Kanbayashi T. Decline of CSF orexin (hypocretin) levels in Prader-Willi syndrome. Am J Med Genet A. 2016;170A:1181–6.
25. De Cock VC, Diene G, Molinas C, Masson V, Kieffer I, Mimoun E, Tiberge M, Tauber M. Efficacy of modafinil on excessive daytime sleepiness in Prader--Willi syndrome. Am J Med Genet A. 2011;155:1552–7.

Chapter 19
Rapid-Onset Obesity with Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation (ROHHAD)

Ilya Khaytin, Susan M. Slattery, and Debra E. Weese-Mayer

Case Presentation

A 4-year-old girl presented to her pediatrician due to new onset of urinary incontinence that occurred twice in a single day, more than 2 years after successful toilet training. In retrospect, her parents reported increased urinary frequency over the prior 3 months, sometimes urinating more than once per hour. They also offered that their daughter had gained 12 pounds over the prior 2 months with development of a more protuberant abdomen and need for larger shoes because her shoes seemed "tighter." Despite these changes, the girl was not particularly bothered, and, notably, she did not complain of any pain or discomfort on urination. Curiously, she reported that her skin was "itchy." The child was less cheerful than her usual upbeat affect. The parents specifically denied any changes in environmental exposures, family dynamics, behavior, or sleep pattern (no snoring or pauses) and no introduction of new stressors.

I. Khaytin (✉)
Division of Pediatric Autonomic Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago and Stanley Manne Children's Research Institute, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
e-mail: ikhaytin@luriechildrens.org, ilya.khaytin@northwestern.edu

S. M. Slattery
Division of Pediatric Autonomic Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago and Stanley Manne Children's Research Institute, Chicago, IL, USA

Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Division of Neonatology, Ann & Robert H. Lurie Children's Hospital of Chicago and Stanley Manne Children's Research Institute, Chicago, IL, USA
e-mail: sslattery@luriechildrens.org, susan.slattery@northwestern.edu

D. E. Weese-Mayer
Division of Neonatology, Ann & Robert H. Lurie Children's Hospital of Chicago and Stanley Manne Children's Research Institute, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
e-mail: dweese-mayer@luriechildrens.org, d-weese-mayer@northwestern.edu

C. Won (ed.), *Complex Sleep Breathing Disorders*,
https://doi.org/10.1007/978-3-030-57942-5_19

Physical exam revealed a chatty, visibly overweight 4-year-old girl in no apparent distress. Her respiratory rate seemed mildly elevated as did her heart rate, but her blood pressure was normal. Her tympanic temperature was mildly reduced at 35.5 °C. Head exam revealed facial fullness, a flattened profile, a boxy shaped configuration, the "lip trait" (lateral one-third of the upper vermilion border is flesh-colored instead of pink), large pupils at rest that seemed sluggish in response to light, adequate dentition, and slightly enlarged tonsils. Ear exam was unremarkable. Chest exam revealed symmetric chest excursion with tidal breathing and excellent aeration in all lung fields on auscultation. Cardiac exam revealed normal heart sounds without murmur and without radial-pedal delay. The hands and feet were cold to the touch. On abdominal exam, protuberance across the level of the umbilicus was apparent, but without overt organ enlargement by palpation and percussion and without a fluid wave. Bowel sounds were active on auscultation. Her neurological exam revealed intact cranial nerves II–XII (except for slow pupillary response to light) and normal tone, strength, and reflexes of the upper and lower extremities. Her musculoskeletal exam revealed mild puffiness of the hands and feet bilaterally. On skin exam, she had protuberance of the upper back suggestive of a subtle buffalo hump but no striae or acanthosis nigricans. Urinalysis and urine culture were negative. An abdominal ultrasound did not reveal any bladder or kidney abnormalities that might account for the recent onset enuresis.

Due to puffy and ice-cold extremities, she was referred to cardiology. Electrocardiogram and echocardiogram were unremarkable, except for an incidental finding of a small patent foramen ovale. She was admitted for further evaluation. Bloodwork including electrolyte and lipid profile was abnormal, including sodium 152 (normal 132–145) mmol/L, chloride 113 (normal 96–108) mmol/L, cholesterol 234 (normal 90–199) mg/dL, triglycerides 512 (normal 32–99) mg/dL, lactate dehydrogenase 325 (normal 50–242) U/L, and morning cortisol 28.3 (normal 6.2–19.4) ug/dL. A magnetic resonance imaging (MRI) of the brain (the hypothalamic sequence) was completed to rule out the possibility of a pituitary tumor causing possible diabetes insipidus and described mood change; no abnormalities were identified, and the normal pituitary "bright spot" was noted. Endocrinology was consulted and ordered a dexamethasone suppression test which was interpreted as indicative of "adequate suppression." Additionally, they noted unremarkable growth hormone and thyroid assessments, but elevated prolactin level of 50 (normal 2–14) ng/mL.

At this point, MRI of the abdomen and pelvis was performed and revealed a 1.5 cm right adrenal mass. On laparoscopy for a right adrenalectomy, the tumor was identified, and on pathologic analysis it was described as a maturing ganglioneuroma and intermixed ganglioneuroblastoma. With sedation and anesthesia, the child demonstrated mild hypoxemia (nadir pulse oximetry (SpO_2) 89%) and moderate hypercarbia (peak end-tidal carbon dioxide (E_TCO_2) 54 mmHg), without any documented change in breathing (no increase in rate or depth despite the physiologic compromise). Repeat labs on postoperative day two included morning cortisol of 9.6 (normal 2.3–19.4) ug/dL and sodium 148 (normal 132–145) mmol/L. However, bloodwork one month later revealed elevated sodium of 159 mmol/L, prolactin of 75 ng/mL, insulin-like growth factor-3 (IGF-3) 4.9 (normal 1–5.2) ng/mL, IGF-1

153 (normal 74–202) ng/mL, and thyroxine (T4) 0.98 (normal 0.8–1.5) ng/mL. Weight gain continued despite the restriction of caloric intake and efforts at increasing daily exercise, such that the child was already 20 pounds above her weight at the initial presentation.

Due to growing suspicion for a condition previously described as central hypoventilation with hypothalamic dysfunction, a polysomnography study was performed. The study revealed transient periods when her oxygen saturation decreased to 91% with an accompanying increase in E_TCO_2 to 49 mmHg, though she did not meet the criteria for hypoventilation, nor did she have any central, obstructive, or mixed apneas. Despite the mild desaturation and hypercarbia, there were no changes in her respiratory effort or her already mildly elevated respiratory rate and heart rate. While asleep the child's heart rate decreased to 45 beats/min intermittently, and her tympanic temperature was consistently 35 °C. During varied age-appropriate activities of daily living awake, SpO_2 values were consistently 93–95%, but E_TCO_2 values rose above 50 mmHg with significant exertion. Because of the nocturnal bradycardia, a 72-h Holter monitoring was performed and was without any abnormalities. Because of concern that the child might have congenital central hypoventilation syndrome (CCHS), stepwise *PHOX2B* testing was performed (Screening Test, then Sequencing Test, then Deletion/Duplication Multiplex Ligation-Dependent Probe Amplification (MLPA) testing) but did not reveal any mutations in the *PHOX2B* gene. Before discharge, urine osmolarity was 821 (normal 50–1200) mOsm/kg and serum osmolarity was 343 (normal 285–295) mOsm/kg, suggesting partial diabetes insipidus. Consequently, desmopressin was initiated as well as a restricted-calorie diet, with a moderate daily activity recommendation to burn calories. The patient was discharged home with close endocrinology follow-up and weekly sodium level checks.

Three months after the initial presentation, the patient's mother noticed that the child was snoring during sleep. A second polysomnography study revealed moderate obstructive sleep apnea with an obstructive apnea-hypopnea index (AHI) of 7.2 events/h and an oxygen saturation nadir of 81%. The central AHI was 2 events/h. The child spent 26% of total sleep time with E_TCO_2 above 50 mmHg. In the absence of adenotonsillar enlargement, non-invasive full-face mask ventilation was initiated and successfully improved oxygenation and ventilation with settings of inspiratory positive airway pressure (IPAP) 8 cmH_2O and expiratory positive airway pressure (EPAP) of 4 cmH_2O. However, despite best efforts, the child continued to gain weight, now reaching 30 pounds more than her weight preceding the initial presentation. On a third sleep study, done one month after the second polysomnography, the child demonstrated central apnea predominance with central AHI of 22 events/h. Consequently, her bi-level mask ventilation via Trilogy ventilator was changed to 12/6 cmH_2O with a rate of 18 breaths/min (bpm). Exogenous ventilatory challenge testing was performed during wakefulness to ascertain the child's peripheral and central chemo-responsiveness. The patient did not increase her rate or depth of breathing, nor did she have any consistent changes in heart rate or blood pressure during 3-min exposures to 100% oxygen, 14% oxygen/7% carbon dioxide, and 5 breaths of 100% nitrogen (Fig. 19.1). This test demonstrated attenuated responses to central and peripheral chemoreflex stimulation. Cerebral near-infrared

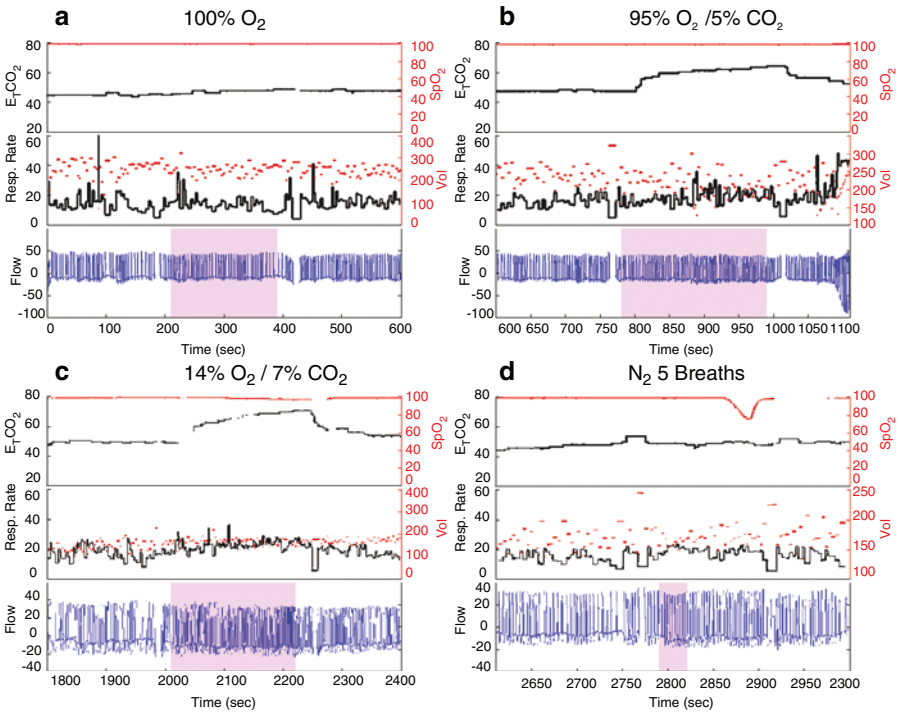


Fig. 19.1 Exogenous ventilatory challenge testing [10] in a 5-year-old child with ROHHAD. Exogenous ventilatory challenge testing evaluates a child's physiologic response to four different inhaled gas mixtures (hyperoxia, hyperoxia/hypercapnia, hypoxia/hypercapnia, and hypoxia). (**a**) During hyperoxia, the child breathes 100% O_2. This test should silence peripheral chemoreceptors. (**b**) During hyperoxia/hypercapnia test, the child breathes 95% fraction of inspired O_2 (FiO_2)/5% fraction of inspired CO_2 ($FiCO_2$). This test should stimulate central chemoreceptors and silence peripheral chemoreceptors. (**c**) During hypoxia/hypercapnia test, the child breathes 14% FiO_2/7% $FiCO_2$. This test should stimulate central and peripheral chemoreceptors. (**d**) During hypoxia/hypercapnia test, the child breathes 100% N_2. This test should stimulate peripheral chemoreceptors. Each challenge is preceded by a 3-min baseline period. The first three challenges (**a**–**c**) are each 3 min in duration. The last challenge (**d**) is 5 breaths long. All challenges are followed by a 3-min recovery period. For all four challenges, the child breathes using a full-face mask and is given modest mechanical ventilator support (LTV 1200 ventilator settings: synchronized intermittent mechanical ventilation/CPAP, respiratory rate (RR) 0 breaths/min (bpm), pressure control (PC) 0 cm water pressure (cmH_2O), pressure support (PS) 10 cmH_2O, and positive end expiratory pressure (PEEP) 0 cmH_2O) to maintain normal SpO_2 and normal E_TCO_2 levels prior to each challenge. *E_TCO_2* end-tidal CO_2 (mmHg), *Resp. Rate* respiratory rate (bpm), *Flow* ventilatory flow (L/min), *SpO_2* peripheral oxygen saturation (%), *Vol* tidal volume (mL)

spectroscopy (cNIRS) waveform decreased during the 14% oxygen/7% carbon dioxide challenge (rather than the expected increase), and only at the third minute of exposure did the cNIRS signal increase, with the increase sustained into the first minute of recovery, collectively indicating aberrant cerebral oxygenation/regional blood flow. Three and one-half months after the initial presentation, the child demonstrated overt hypoventilation throughout all sleep time, with saturation nadir of 85%, with values below 92% during 50% of the sleep time, and peak E_TCO_2 of

58 mmHg with values above 50 mmHg during 100% of the sleep time, while asleep breathing spontaneously. Efforts to improve oxygenation and ventilation with a bi-level face mask and with nose mask ventilation and a Trilogy ventilator were unsuccessful, so a tracheostomy was placed, and mechanical ventilation during sleep was instituted using pressure ventilation.

Based on the characteristic weight gain of 20–30 pounds over a 3–6 month period, the laboratory test results supportive of evolving hypothalamic dysfunction, the hypoventilation, and the symptoms compatible with autonomic dysregulation (dilated pupils, ice-cold hands and feet, reduced core temperature, altered control of breathing), this child was diagnosed with ROHHAD (rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation) with a benign neural crest tumor.

Discussion

History of ROHHAD

ROHHAD was first described in 1965 by Fishman et al. [1] but with the literary misnomer "primary alveolar hypoventilation syndrome (Ondine's curse)." Few cases were reported between 1965 and 2000 when Katz et al. introduced the term "late-onset central hypoventilation syndrome with hypothalamic dysfunction (LO-CHS/HD)" [2], described the 11th case ever reported in the literature, and suggested it was likely distinct from CCHS. And in 2007, Ize-Ludlow et al. introduced the acronym that refers to the characteristic order of phenotype presentation: rapid-onset obesity with hypothalamic dysfunction, hypoventilation and autonomic dysregulation (ROHHAD) [3]. That paper reported on 23 children with ROHHAD, including 15 that had detailed reporting and the absence of a CCHS-related *PHOX2B* mutation and including 5 with a benign tumor of neural crest origin. Bougneres et al. later suggested adding the suffix "NET" to the ROHHAD acronym [4], though this term is rarely applied. ROHHAD is a rare neurocristopathy with fewer than 200 cases reported in the literature or in our practice. As the name implies, it affects multiple organ systems and, if unrecognized or untreated with conservative management and anticipation of the phenotypic features as they unfold with advancing age, can lead to severe morbidity and mortality.

Etiology

Despite extensive investigation, no genetic signature of ROHHAD has been identified to date [5–8]. The similarities in respiratory and autonomic features between ROHHAD and CCHS are striking. However, to date, no child with ROHHAD had an identified CCHS-related *PHOX2B* gene mutation on fragment analysis, sequence analysis, or duplication/deletion analysis. Variants in several genes have been

interrogated, including BDNF [3], TRKB [3], ACSL1 [7], NECDIN [7], HTR1A [9], OTP [9], PACAP [9], and HCRT [6], but none were identified as disease-defining for ROHHAD.

Presentation

As defined in 2007 by Ize-Ludlow et al., patients with ROHHAD are previously seemingly normal until between the ages of 2 and 7 years when they develop a unique constellation of symptoms heralded typically by rapid weight gain of 20–30 pounds over a 4–6-month period. Subsequently, the child will develop features of hypothalamic dysfunction then hypoventilation and altered autonomic function. A subset of the patients will have a respiratory arrest and/or a tumor of neural crest origin. Importantly, the presence of a CCHS-related *PHOX2B* mutation excludes the diagnosis of ROHHAD. With each of the key phenotypic features, there is a range to the severity of the symptoms. Usually, the first symptom is rapid weight gain. Because this happens in children who have recently acquired independent mobility with increased appetite, often this rapid weight gain is either attributed to change in diet or overlooked altogether until other symptoms emerge. However, the rate at which children gain weight is often dramatic and atypical for other causes of early obesity. Other early symptoms occasionally include behavioral problems such as irritability and aggression or hyperactivity. Again, these problems are common in the general pediatric population at this age and often do not lead to consideration of a ROHHAD diagnosis.

Weight gain and behavioral problems may be the only abnormalities for months, though the behavioral issues often resolve after the hypoventilation is properly treated. More typically, just like in the case discussed in this chapter, the initial weight gain is followed by endocrine abnormalities that gradually unfold with advancing age—at initial visits all of the endocrine abnormalities are not yet manifest. Rarely, polydipsia and polyuria develop. Some children may develop secondary enuresis after a period of being toilet trained. Hypernatremia is not infrequently reported, and partial diabetes insipidus is often diagnosed. The workup usually leads to the discovery of hypernatremia and occasionally hypothyroidism. On subsequent evaluations, IGF-1 and IGF-3 levels may be reduced, and the growth hormone stimulation test may be abnormal with a decreased response (<10 ng/mL). Prolactin levels are elevated in nearly all patients with ROHHAD, with identification very early in the course of illness. Children may also demonstrate precocious puberty and premature adrenarche.

In addition to weight gain and endocrine abnormalities, children with ROHHAD develop features of autonomic nervous system dysregulation (ANSD), with symptoms gradually unfolding over months to years, sometimes delaying definitive diagnosis. Ophthalmologic manifestation with strabismus, light sensitivity, and delayed pupillary response compared to normal-weight controls but not obese controls are most common. Less frequent are an inability to produce tears, ptosis, and oculomotor apraxia. Parents are often alarmed by the ice-cold and puffy hands and feet. Over

time, they also may notice decreased or excessive sweating. Constipation is common, though occasionally diarrhea and vomiting may be observed. Children with ROHHAD rarely report pain in response to accidental trauma or phlebotomy, suggesting an increased pain threshold (Table 19.1).

Table 19.1 Clinical presentation of children with ROHHAD

Clinical findings	% of patients	Clinical findings	% of patients
Hypothalamic dysfunction		*Autonomic dysregulation (cont)*	
Rapid-onset obesity	100%	Altered sweating	53%
Failed growth hormone stimulation test	60%	Cold hand and feet	40%
Hyperphagia	53%	Bradycardia	33%
Polydipsia	53%	Tumors of neural crest origin	33%
Hypernatremia	47%	Syncopal episodes	7%
Hyperprolactinemia	47%	*Other findings*	
Diabetes insipidus	33%	Altered perception of pain	53%
Hypothyroidism	33%	Seizure	33%
Adrenal insufficiency	27%	Enuresis	27%
Hypodipsia	27%	Hypotonia	27%
Polyuria	27%	Hypercholesterolemia	20%
Short stature	20%	Scoliosis	20%
Delayed puberty	13%	Hypersomnolence	13%
Hyponatremia	13%	Recurrent pneumonia	13%
Low IGF-1 and IGFBP-3 levels	13%	Impaired glucose tolerance	6%
Precocious puberty	13%	Type 2 diabetes mellitus	6%
Premature adrenarche	13%	*Developmental disorder*	
Transient SIADH	13%	Developmental delay	20%
Amenorrhea	7%	Developmental regression	20%
Hypogonadotropic hypogonadism	7%	*Behavioral disorders*	
Irregular menses	7%	Depression	13%
Transient diabetes insipidus	7%	Flat affect	13%
Respiratory manifestations		Psychosis	13%
Alveolar hypoventilation	100%	Behavioral outbursts	7%
Cardiorespiratory arrest	60%	Bipolar disorder	7%
Reduced CO_2 ventilatory response	60%	Emotional lability	7%
Obstructive sleep apnea	53%	Obsessive-compulsive disorder	7%
Cyanotic episodes	27%	Oppositional-defiant disorder	7%
Autonomic dysregulation		Tourette's syndrome	7%
Ophthalmologic manifestations	87%	Hallucinations	7%
Thermal dysregulation	73%		
Gastrointestinal dysmotility	67%		

Modified from Ize-Ludlow et al. [3]
SIADH syndrome of inappropriate antidiuretic hormone secretion, *IGF* insulin-like growth factor, *IGFB* insulin-like growth factor-binding protein, *ADHD* attention-deficit/hyperactivity disorder

Endocrine abnormalities are usually temporally followed by respiratory abnormalities (in the absence of primary lung disease) and ANSD. Obstructive sleep apnea is a relatively common presentation. Polysomnography studies demonstrate mild to severe obstructive sleep apnea, but often the initial sleep study does not show significant hypoventilation. However, all children with ROHHAD will develop hypoventilation over the next months to years. The exogenous ventilatory challenge [10] at the time of presentation often does not demonstrate significant abnormalities, but over time attenuated peripheral and central chemoreceptor responses emerge [10]. The central hypoventilation becomes a major risk factor for cardiorespiratory arrest and requires anticipation, prompt identification, and artificial ventilation as life support. It is important to note that as the ROHHAD phenotype unfolds, the child may develop awake hypoventilation as well, which may be missed in children who only undergo nighttime physiologic evaluations. A parental report that the child is a "great swimmer" who can hold her breath for a long time should alert a physician to the possibility of abnormal control of breathing. Exogenous ventilatory challenge testing demonstrates a decreased response to hypercarbia and hypoxemia; however, it is not as severe as in children with CCHS [10]. In the known children with ROHHAD, earlier onset of symptoms often correlates with more severe hypoventilation, requiring more aggressive management [3]. Unfortunately, a cardiorespiratory arrest occurs in half of the diagnosed patients. Often the cardiorespiratory arrest is preceded by unrecognized sleep-hypoxemia and obstructive or hypopnea events.

Additionally, as in this patient, tumors of neuroendocrine origin are seen in approximately 40% of children [3, 8]. Ganglioneuromas and ganglioneuroblastomas are most common, though neuroblastoma has been occasionally reported, all potentially occurring anywhere along the sympathetic chain or in either adrenal gland.

Differential Diagnosis

It is important to distinguish ROHHAD from other disorders with overlapping clinical features. As noted above, ROHHAD shares some features with CCHS; however, most children with CCHS present during the first few days to weeks of life, are not obese and have a more severe control of breathing deficit, with markedly attenuated peripheral and central chemoreceptor responsiveness (compared to patients with ROHHAD). Later-onset CCHS (LO-CCHS) is diagnosed after 1 month of age and often later into childhood and adulthood, but these patients are not obese, either. Patients with CCHS and LO-CCHS have a *PHOX2B* gene mutation that is implicit to the diagnosis. Another disorder with autonomic features and excessive weight gain is Prader-Willi syndrome. However, children with Prader-Willi will present in the neonatal period with hypotonia and severe developmental delay occurring in the first year of life, while children with ROHHAD have average full-scale IQ except for the subset of patients who have experienced respiratory arrest with delayed

resuscitation [11]. Unlike ROHHAD [12], Prader-Willi syndrome has a genetic marker on chromosome 15 (15q11.2–q13). Also, children with Prader-Willi syndrome usually have growth hormone insufficiency but not hyperprolactinemia [12]. ROHHAD-related hypoventilation does not usually respond to weight loss, distinguishing it from obesity hypoventilation. ROHHAD is distinct from obesity hypoventilation [13, 14] in terms of the weight gain trajectory, age of presentation, presence of obstructive sleep apnea then alveolar hypoventilation after intervention for the OSA, unfolding of the phenotype such that the findings evolve with advancing age, varied severity of hypothalamic dysfunction, and association of a (typically) benign neural crest tumor.

Management

A timely diagnosis of ROHHAD is essential to optimize the outcome for these especially vulnerable children. Management of children with ROHHAD depends on early diagnosis. Any young child with rapid-onset obesity with hypothalamic abnormalities must be suspected of having ROHHAD. Once ROHHAD is diagnosed, children require very close monitoring and anticipatory management. Day and night time evaluations of cardiorespiratory function and autonomic regulation should be performed and initially repeated every 6 months to determine the appropriate level of ventilatory support. All children with ROHHAD require support at least during sleep, and most need continuous artificial ventilatory support awake and asleep. Many children with ROHHAD benefit from tracheostomy with mechanical ventilation to implement a safe airway and provide life support. Patients who only require nocturnal support may benefit from non-invasive ventilation with a home ventilator, though stability of the airway may be limited. Phrenic nerve-diaphragm pacing is not likely to be effective in children with ROHHAD because of the extreme amount of adipose tissue between the surgically implanted receiver and the external radiofrequency board/antennae and the need to move excessive weight with each paced excursion of the diaphragm. If pacing is considered in a patient with ROHHAD, it would demand a patent tracheostomy and should never be used during sleep or with a capped tracheostomy tube due to a risk of very severe obstructive sleep apnea not amendable to tonsillectomy and/or nasopharyngeal surgical procedures [15]. However, no matter which mode of artificial ventilation is most appropriate for a given child, continuous oxygen saturation and end-tidal CO_2 monitoring must be provided, as well as an awake highly trained registered nurse during all of patient's sleep time at a minimum. Since children with ROHHAD do not have intact respiratory control, they are at risk of both hypoxemia and hypocarbia, impacting among other things cerebral regional blood flow and oxygenation. The goal should be maintaining $SpO_2 > 92\%$ and E_TCO_2 in the 30–50 mmHg range. Parents and caregivers should be educated on how to administer cardiopulmonary resuscitation, tracheostomy care, and ventilator management. Aggressive attention to the respiratory needs of ROHHAD patients allows maintaining normal neurocognitive development.

Additionally, all children suspected of ROHHAD should have serial laboratory screening including the following: complete blood count with differential, reticulocyte count, complete metabolic panel, serum and urine osmolality, prolactin and macroprolactin levels, leptin, free thyroxine, thyroid-stimulating hormone, Insulin-like Growth Factor-binding Protein and Insulin-like Growth Factor I levels, lipid screen, and cortisol levels. MRI of the brain to exclude hypothalamic-pituitary abnormalities is also recommended. An endocrinologist familiar with ROHHAD can be an invaluable asset in helping these children.

Considering the frequency of cardiorespiratory arrest, electrocardiogram and 72-h Holter monitoring are necessary. Echocardiogram is essential to evaluate for *cor pulmonale* and/or right ventricular hypertrophy due to anticipated intermittent hypoxia. Because of the extreme bradycardia during sleep, a very small subset of patients has received implanted cardiac pacemakers.

All children with suspected ROHHAD should have abdominal and chest imaging done to survey for neural crest tumors, initially including chest X-ray and abdominal/pelvic ultrasound. Found early, these tumors are amenable to surgical treatment. Though recurrence has not been reported in the literature, it is reasonable to continue surveillance with advancing age. Notably, tumor removal does not resolve the symptoms of ROHHAD.

Considering reported behavioral problems, the innate control of breathing deficit, and the risk of recurrent hypoxemia and hypercarbia, it is prudent to perform annual neurocognitive testing. With an enriched educational environment and conservative ventilatory management, children with ROHHAD can have normal development. Children who are managed aggressively appear to do better neurocognitively and have a better quality of life. Early involvement of a pediatric psychologist familiar with the management of children with chronic disease and ventilatory support is an important member of the healthcare team to help the patients and their families to cope with the ROHHAD phenotype.

To date, there are only a few case reports describing use of pharmacotherapy in ROHHAD. Cyclophosphamide [16] and rituximab [16] were used in a few cases, but their success was limited. There is a report of improved metabolic rate and respiratory function with caffeine [17]. Steroids [18] and growth hormone replacement [19] have been described.

Ultimately, a high index of suspicion for ROHHAD in children with rapid-onset obesity and hypothalamic problems can result in earlier diagnosis and ideally a better outcome. At present, there is no cure for ROHHAD, but limited reports show that it often stabilizes and sometimes even improves over time with optimal management.

Clinical Pearls

- Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) is a rare disorder, which can result in cardiorespiratory arrest if not diagnosed and managed in a timely manner.
- There is no genetic test for ROHHAD at present. Stepwise testing for a CCHS-related *PHOX2B* mutation excludes the diagnosis of CCHS.

- Any previously healthy and non-obese child who rapidly gains 20–30 pounds between ages 2 and 7 years, followed by evidence of endocrine abnormalities, should be evaluated for evidence of ROHHAD. As the whole phenotype of the disorder may not be evident at the onset, a high index of suspicion must be maintained.
- It is important to evaluate the child for any evidence of hypoventilation during wakefulness and sleep. If present, the child will need ventilatory support to prevent cardiorespiratory arrest. Both oxygen saturation and end-tidal CO_2 must be monitored and the ventilatory settings adjusted to maintain optimal gas exchange.
- Echocardiography and electrocardiogram should be performed every 6 months to evaluate for *cor pulmonale* and/or right ventricular hypertrophy due to anticipated intermittent hypoxia.
- 72-h Holter monitoring should be performed every 6 months to evaluate for severe bradycardia.
- Since neural crest tumors occur in approximately half of the children with ROHHAD, they should have serial chest and abdomen/pelvis imaging (chest X-ray and abdominal/pelvic ultrasound) every 6 months. Found early, these tumors are amenable to surgical treatment.
- The patient with ROHHAD will need to be closely followed in terms of ventilatory status and endocrine abnormalities, initially every 3 months then as the rate of change diminishes every 6 months and eventually every year. The patient will need to have aggressive management of weight to prevent further worsening of obesity.
- There is currently no cure for ROHHAD; however, with optimal management, disease burden can be reduced for children with ROHHAD. There is anecdotal evidence that the severity of the ROHHAD phenotype may decrease as the child grows older.

References

1. Fishman LS, Samson JH, Sperling DR. Primary alveolar hypoventilation syndrome (Ondine's curse). Am J Dis Child. 1965;110:155–61.
2. Katz ES, McGrath S, Marcus CL. Late-onset central hypoventilation with hypothalamic dysfunction: a distinct clinical syndrome. Pediatr Pulmonol. 2000;29(1):62–8.
3. Ize-Ludlow D, Gray JA, Sperling MA, et al. Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation presenting in childhood. Pediatrics. 2007;120(1):e179–88.
4. Bougneres P, Pantalone L, Linglart A, Rothenbuhler A, Le Stunff C. Endocrine manifestations of the rapid-onset obesity with hypoventilation, hypothalamic, autonomic dysregulation, and neural tumor syndrome in childhood. J Clin Endocrinol Metab. 2008;93(10):3971–80.
5. Barclay SF, Rand CM, Borch LA, et al. Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD): exome sequencing of trios, monozygotic twins and tumours. Orphanet J Rare Dis. 2015;10:103.

6. Barclay SF, Rand CM, Gray PA, et al. Absence of mutations in HCRT, HCRTR1 and HCRTR2 in patients with ROHHAD. Respir Physiol Neurobiol. 2016;221:59–63.
7. De Pontual L, Trochet D, Caillat-Zucman S, et al. Delineation of late onset hypoventilation associated with hypothalamic dysfunction syndrome. Pediatr Res. 2008;64(6):689–94.
8. Lee JM, Shin J, Kim S, et al. Rapid-onset obesity with hypoventilation, hypothalamic, autonomic dysregulation, and neuroendocrine tumors (ROHHADNET) syndrome: a systematic review. Biomed Res Int. 2018;2018:1250721.
9. Rand CM, Patwari PP, Rodikova EA, et al. Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation: analysis of hypothalamic and autonomic candidate genes. Pediatr Res. 2011;70(4):375–8.
10. Carroll MS, Patwari PP, Kenny AS, Brogadir CD, Stewart TM, Weese-Mayer DE. Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD): response to ventilatory challenges. Pediatr Pulmonol. 2015;50(12):1336–45.
11. Warner JJ, Zelko FA, Weese-Mayer DE. Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD): dichotomy of neurocognitive performance. Am J Respir Crit Care Med. 2018;197:A1993.
12. Barclay SF, Rand CM, Nguyen L, et al. ROHHAD and Prader-Willi syndrome (PWS): clinical and genetic comparison. Orphanet J Rare Dis. 2018;13(1):124.
13. Mokhlesi B. Obesity hypoventilation syndrome: a state-of-the-art review. Respir Care. 2010;55(10):1347–62; discussion 1363–1345.
14. Piper AJ, Grunstein RR. Obesity hypoventilation syndrome: mechanisms and management. Am J Respir Crit Care Med. 2011;183(3):292–8.
15. Ballard HA, Leavitt OS, Chin AC, et al. Perioperative anesthetic management of children with congenital central hypoventilation syndrome and rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation undergoing thoracoscopic phrenic nerve-diaphragm pacemaker implantation. Paediatr Anaesth. 2018;28(11):963–73.
16. Jacobson LA, Rane S, McReynolds LJ, Steppan DA, Chen AR, Paz-Priel I. Improved behavior and neuropsychological function in children with ROHHAD after high-dose cyclophosphamide. Pediatrics. 2016;138(1):e20151080.
17. Gordon SC, Rand CM, Stewart T, et al. The evolving phenotype in a patient with rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) and response to caffeine treatment. Am J Respir Crit Care Med. 2015;191:A5923. Presented at American Thoracic Society International Conference, Denver, Colorado, May 2015.
18. Chow C, Fortier MV, Das L, et al. Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) syndrome may have a hypothalamus-periaqueductal gray localization. Pediatr Neurol. 2015;52(5):521–5.
19. Jalal Eldin AW, Tombayoglu D, Butz L, et al. Natural history of ROHHAD syndrome: development of severe insulin resistance and fatty liver disease over time. Clin Diabetes Endocrinol. 2019;5:9.

Chapter 20
Chiari Malformations

Mustafa Bseikri and Shannon S. Sullivan

Case

A 12-year-old boy with medical history notable for allergic rhinitis presents to his pediatrician with parental complaints of headaches, snoring, and non-restorative sleep. He reports some intermittent headaches, most commonly frontal in location. His headaches were further elucidated as also having a posterior component, which could be aggravated by coughing or sneezing. He experienced headaches most days. He denied difficulty swallowing or gait disturbance.

Family has noticed him waking up gasping at times during sleep. There is a maternal history of obstructive sleep apnea. On examination, his BMI is at the 69th percentile for age. He is noted to have 2+ tonsils with minimal inferior turbinate hypertrophy. Physical examination demonstrated normal cranial nerve exam, symmetric upper and lower extremity strength, and normal gait. Patellar reflexes were normal.

Given concerns for possible obstructive sleep apnea, an attended polysomnography (PSG) was obtained. Nocturnal PSG (Fig. 20.1) was notable for apnea-hypopnea index (AHI) of 9.3/h with a predominance of central apneas (central apnea index of 7.4/h). Some intermittent snoring was observed. The SpO_2 nadir was 85%, with an 3% oxygen desaturation index (ODI) 10.9/h, and time with pulse oximetry oxygen saturation (SpO_2) <90% of 0.7 min. Relative bradypnea was noted, with a baseline respiratory rate of 7–8 breaths/min. There was no evidence of sleep-related hypoventilation by surrogate measure, with baseline transcutaneous carbon dioxide ($TcCO_2$) levels of 37–38 mmHg and maximum $TcCO_2$ of 46 mmHg.

M. Bseikri
Pediatric Pulmonary & Sleep Medicine, Kaiser Permanente – Northern California, Northern California, CA, USA

S. S. Sullivan (✉)
Pediatric Pulmonary & Sleep Medicine, Stanford University, Palo Alto, CA, USA
e-mail: shannon.s.sullivan@stanford.edu

C. Won (ed.), *Complex Sleep Breathing Disorders*,
https://doi.org/10.1007/978-3-030-57942-5_20

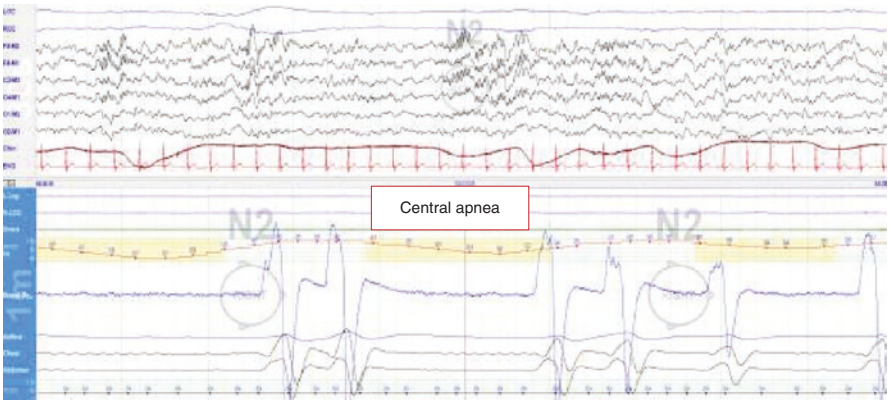


Fig. 20.1 Polysomnography (EOG, EEG, chin EMG, and ECG at 30 s, remainder of signals at 60 s) demonstrating bradypnea and central apneas with associated desaturation during N2 sleep. *EOG* electrooculography, *EEG* electroencephalography, *EMG* electromyography, *ECG* electrocardiography, *N2* non-rapid eye movement sleep stage 2, *nasal pressure* nasal flow measured by a nasal pressure transducer, *Airflow* flow measured by thermistor, *Chest* chest movement measured by plethysmography, *Abdomen* abdominal movement measured by plethysmography, $TcCO_2$ transcutaneous carbon dioxide

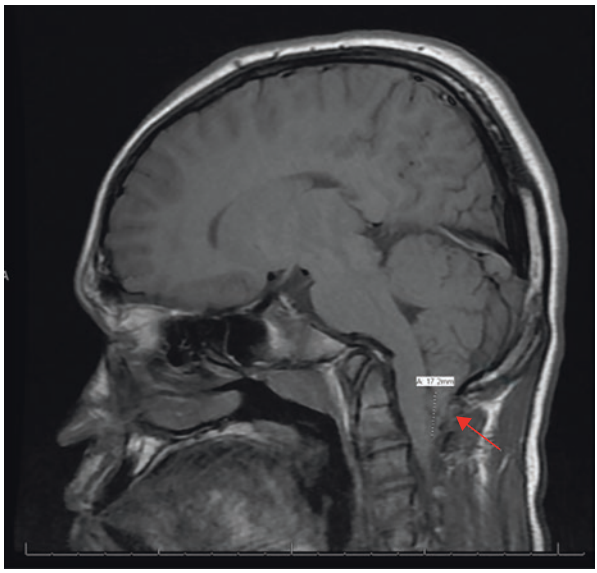


Fig. 20.2 MRI of the brain, demonstrating protrusion of the cerebellar tonsils below the foramen magnum (red arrow)

Given the predominance of central apneas, concern for central nervous system pathology was raised, and magnetic resonance imaging (MRI) of the brain was ordered (Fig. 20.2). This was notable for pointed cerebellar tonsils extending 17 mm below the foramen magnum. MRI of the cervical, thoracic, and lumbar spine was suggestive of a possible small developing syrinx versus dilated central canal in the

upper cervical cord. The patient was subsequently referred for neurosurgical consultation. Given the presence of headaches and central sleep apnea resulting in symptomatic sleep disturbance, the patient was scheduled for surgical decompression with suboccipital craniectomy, laminectomy, and expansile duraplasty.

Following surgery, the patient had an uneventful post-operative course and was discharged home on post-operative day two. On follow-up visit 1 month after surgery, family noticed a decrease in snoring and more refreshing sleep. Headaches, including the post-tussive component, had also improved.

Follow-up MRI of the brain after 4 months demonstrated improved crowding of the foramen magnum, with resolution of the possible small developing syrinx. Repeat diagnostic polysomnography demonstrated improvement in both central and obstructive apnea indices, with an overall AHI of 1.9/h and central apnea index of 1.2/h, and saturation nadir of 92%. No significant snoring was noted.

Discussion

Chiari malformations (CM) are a heterogeneous group of hindbrain disorders at the craniocervical junction, characterized by caudal displacement of the portions of the cerebellum beyond the foramen magnum [1]. Several subtypes have been described based on the associated findings, with most cases classified as either Chiari I (CM1) or Chiari II (CM2) malformations. CM1 malformations involve cerebellar tonsillar protrusion >5 mm below the foramen magnum [2], whereas CM2 (also termed Arnold-Chiari) malformations are associated with more pronounced displacement of the cerebellar vermis, as well as herniation of the medulla and fourth ventricle through the foramen magnum into the cervical spinal canal [3], and often associated with the presence of a myelomeningocele [4]. Tonsillar herniation itself may be due to a variety of underlying pathologies which must be considered during work-up, including insufficient posterior fossa volume, cerebral spinal fluid outflow obstruction, increased intracranial pressure from supratentorial sources, or instability at the craniocervical junction, for example, due to connective tissue disease [5].

CM1 often presents during the second decade of life, but may not be diagnosed until adulthood [5, 6]. Signs and symptoms prompting a work-up and eventual diagnosis of CM1 may include headache (often exacerbated by cough or sneezing), syncope (associated with Valsalva maneuver), vocal cord paralysis, ataxia, scoliosis, neck pain, and sleep disordered breathing (SDB) [6]. Some individuals with CM1 may be asymptomatic, with a normal neurologic exam, and the defect may be only identified incidentally on neuroimaging. For example, at a single center reporting 1073 pediatric patients identified with CM over two decades, 620 were identified incidentally on radiography [5]. When present, abnormal physical exam findings may include downbeat nystagmus, poor oromotor function, and voice change associated with vocal cord dysfunction, as well as abnormal gag and tendon reflexes [3].

Conversely, CM2 is often identified perinatally due to the frequent presence of myelomeningocele and resultant paralysis below the level of the lesion [7].

Hydrocephalus is also frequently identified due to cerebral spinal fluid obstruction. Diagnosis is based on neuroimaging, with MRI of the brain as the most common diagnostic modality [8].

Sleep disordered breathing is a common finding in individuals with CM and can present with obstructive sleep apnea (OSA), central sleep apnea (CSA), and/or mixed apneas. While the exact prevalence of SDB in CM is unclear, an analysis of multiple small studies of SDB in CMs estimates a prevalence of 63–70% [9]. The development of CSA may be due to dysfunction of brainstem respiratory centers, thought to be due to compression of brainstem respiratory centers in the medulla oblongata and areas important for tone of the upper airway [10] or possibly compression of the vasculature and subsequent ischemia in the medulla [11]. Other potential mechanisms include compression of the brainstem leading to negative impacts upon the reticular activating system and compression or stretching of the glossopharyngeal nerve with subsequent impairment of afferent input from the carotid bodies, impairing chemoreflexes or decreasing responsiveness to arterial carbon dioxide [9]. Additionally, individuals with CM have been demonstrated to have a reduction in several cephalometric parameters, including length and thickness of the soft palate, as well as an overall reduction in oral cavity area that may also predispose to the increased prevalence of OSA [12].

While CSA (as opposed to OSA) may have traditionally been associated with CM, more recent studies demonstrate a more varied presentation regarding the prevalence of OSA and CSA in individuals with CM. Among children with CM in one case series, 62% had evidence of SDB, with only 25% of those demonstrating CSA [13]. A prospective study of 46 individuals with CM reviewed the incidence of CSA and OSA among children and adults [11]. Overall, this study demonstrated that 67% of individuals with CM had evidence of SDB on PSG. Among children, 58% of those with SDB had OSA. Similarly, a majority of adults (78%) with CM and SDB also demonstrated primarily OSA on evaluation by PSG. Interestingly, the presence of vocal cord paralysis was associated with an increased likelihood of central sleep apnea. While many studies have suggested that a minority of individuals with CM and SDB demonstrate CSA, a few have demonstrated the prevalence of CSA as high as 94% [14]. It has been suggested that OSA might be a sign of increased intracranial pressure in those with CMs, though others have argued that in fact OSA may worsen intracranial pressure, which could feed back to worsen the degree of tonsillar herniation or lead to syrinx [15, 16]. Mixed apnea is also reported to be encountered in those with CMs, and it has also been reported that individuals can transition from one variety of apnea to another and improve or transition after therapy [17, 18].

In terms of work-up, certainly the presence of focal neurologic deficits or cardinal symptoms in parallel with the presence of SDB warrants an evaluation for secondary etiologies including CM. Given that both OSA and CSA can be associated with CM, this can pose a diagnostic challenge regarding when to consider neuroimaging based on SDB findings alone.

A retrospective review of 59 children with SDB referred for MRI (due to persistent OSA despite adenotonsillectomy, moderate-severe OSA without adenotonsillar hypertrophy, significant CSA, or nocturnal hypoventilation) demonstrated that 32%

of all children had an abnormal MRI [19]. Among children who were non-syndromic with abnormal MRI, 89% had CM. Abnormal MRI was identified in children with only OSA, only CSA, and mixed sleep apnea, as well as nocturnal hypoventilation. As a result, consideration of neuroimaging may also be warranted in children with SDB, whether CSA or OSA is predominant, and without clear underlying etiology based on history and physical examination. A related interesting question is whether individuals with incidentally discovered CMs should undergo polysomnography; on this there is no consensus. In one prospective study of 53 pediatric and adolescent patients with CM1 [20], 24% had SDB on PSG, though none of the CSA patients and only three of the OSA patients reported symptoms, suggesting that the better part of valor may be to objectively evaluate all patients.

Treatment, too, is an area without clear consensus, and there are no randomized controlled trials to assess treatments for patients with CM1 nor clear therapeutic guidelines [5]. It has been argued that while CMI is primarily thought of in the context of tonsillar herniation, it is the possibility of associated syringomyelia, seen in a reported 30–70% of pediatric patients, which may drive treatment decisions, since a delay in diagnosis may lead to irreversible neurological impacts. The mainstay of treatment for symptomatic CM is posterior fossa decompression (PFD), which has been associated with improvements in SDB on post-operative PSG [5]. PFD may consist of suboccipital craniectomy, possibly also with laminectomy, shunts, or duraplasty [21]. Among the key questions are patient selection for PFD; generally, this series of procedures are reserved for symptomatic patients. Some insight can be gained from a retrospective study [22] of 147 pediatric CM1 patients not undergoing surgery, followed for a mean of 3.8 years by imaging and 4.6 years clinically, which indicated that generally the course is benign with some cases of spontaneous improvement and other cases of worsening. In fact the degree of SDB is highly variable in the CM population, increasing uncertainty about who requires treatment. Furthermore, the results of PFD are also variable. While clear improvements in SDB have been demonstrated, resolution may be incomplete, possibly related to permanent damage of compressed brainstem centers [23].

Beyond PFD, other therapies have been reported in CM patients. Continuous positive airway pressure (CPAP), bilevel positive airway pressure (BPAP), and BPAP with backup rate in timed mode (i.e., BPAP-ST) have all been reported to offer some improvement [18, 24]. If adenotonsillar hypertrophy is present, adenotonsillectomy can be considered in those with demonstrated OSA, though post-operative PSG is recommended in all children with CMs undergoing surgery due to variable response to treatment. Interestingly, while some reports indicate gradual improvement of SDB after surgeries, some case reports also indicate that recurrence after PFD surgery is possible [25]. Because of reported increased risk of recurrence or worsening of SDB over time, long-term follow-up of CM patients has been recommended [16].

Ultimately, due to the heterogeneity of radiographic and clinical findings, timing of diagnosis, and variable success of treatments, each case of Chiari malformation must be considered with a multidisciplinary team, which may include pediatric neurology, neurosurgery, pulmonary, and sleep physicians.

Take-Home Points

- Chiari malformations (CM) are a heterogeneous group of hindbrain disorders at the craniocervical junction, characterized by caudal displacement of the portions of the cerebellum beyond the foramen magnum.
- Sleep disordered breathing is common in CM and can take the form of obstructive, central, or mixed sleep apnea, as well as nocturnal hypoventilation.
- Central sleep apnea may develop due to compression of the brainstem or compression of the vasculature to the respiratory centers in the medulla oblongata. There may also be compression of the glossopharyngeal nerve with subsequent impairment of afferent input from the carotid bodies, leading to impaired chemoreflexes and decreased responsiveness to arterial carbon dioxide. Obstructive sleep apnea may occur due to compression of brainstem areas important for upper airway tone.
- Posterior fossa decompression is considered the mainstay therapy for symptomatic CMs, though PAP therapies and adenotonsillectomy have been reported in select cases.

References

1. Cesmebasi A, Loukas M, Hogan E, Kralovic S, Tubbs RS, Cohen-gadol AA. The Chiari malformations: a review with emphasis on anatomical traits. Clin Anat. 2015;28(2):184–94.
2. Barkovich AJ, Wippold FJ, Sherman JL, Citrin CM. Significance of cerebellar tonsillar position on MR. AJNR Am J Neuroradiol. 1986;7(5):795–9.
3. Chiapparini L, Saletti V, Solero CL, Bruzzone MG, Valentini LG. Neuroradiological diagnosis of Chiari malformations. Neurol Sci. 2011;32(suppl 3):S283–6.
4. Stevenson KL. Chiari type II malformation: past, present, and future. Neurosurg Focus. 2004;16(2):1–7.
5. Alexander H, Tsering D, Myseros JS, Magge SN, Oluigbo C, Sanchez CE, Keating RF. Management of Chiari I malformations: a paradigm in evolution. Childs Nerv Syst. 2019;35:1809–26.
6. Milhorat TH, Chou MW, Trinidad EM, Kula RW, Mandell M, Wolpert C, Speer MC. Chiari I malformation redefined: clinical and radiographic findings for 364 symptomatic patients. Neurosurgery. 1999;44(5):1005–17.
7. McLone DG, Dias MS. The Chiari II malformation: cause and impact. Childs Nerv Syst. 2003;19(7–8):540–50.
8. Piper RJ, Pike M, Harrington R, Magdum SA. Chiari malformations: principles of diagnosis and management. BMJ. 2019;365:l1159.
9. Leu RM. Sleep-related breathing disorders and the Chiari 1 malformation. Chest. 2015;148(5):1346–52. https://doi.org/10.1378/chest.14-3090.
10. Ely EW, McCall WV, Haponik EF. Multifactorial obstructive sleep apnea in a patient with Chiari malformation. J Neurol Sci. 1994;126(2):232–6.
11. Dauvilliers Y, Stal V, Abril B, Coubes P, Bobin S, Touchon J, Escourrou P, Parker F, Bourgin P. Chiari malformation and sleep related breathing disorders. J Neurol Neurosurg Psychiatry. 2007;78(12):1344–8.

12. Urbizu A, Ferré A, Poca MA, Rovira A, Sahuquillo J, Martin BA, Macaya A. Cephalometric oropharynx and oral cavity analysis in Chiari malformation type I: a retrospective case-control study. J Neurosurg. 2017;126(2):626–33.
13. El-Kersh K, Cavallazzi R, Fernandez A, Moeller K, Senthilvel E. Sleep disordered breathing and magnetic resonance imaging findings in children with Chiari malformation type I. Pediatr Neurol. 2017;76:95–6.
14. Henriques-Filho PS, Pratesi R. Sleep apnea and REM sleep behavior disorder in patients with Chiari malformations. Arq Neuropsiquiatr. 2008;66(2B):344–9.
15. Jennum P, Børgesen SE. Intracranial pressure and obstructive sleep apnea. Chest. 1989;95(2):279–83.
16. Luigetti M, Losurdo A, Dittoni S, et al. Improvement of obstructive sleep apneas caused by hydrocephalus associated with Chiari malformation type II following surgery. J Neurosurg Pediatr. 2010;6(4):336–9.
17. Tran K, Hukins CA. Obstructive and central sleep apnoea in Arnold-Chiari malformation: resolution following surgical decompression. Sleep Breath. 2011;15(3):611–3.
18. Levitt P, Cohn MA. Sleep apnea and the Chiari I malformation: case report. Neurosurgery. 1988;23(4):508–10.
19. Selvadurai S, Al-Saleh S, Amin R, Zweerink A, Drake J, Propst EJ, Narang I. Utility of brain MRI in children with sleep-disordered breathing. Laryngoscope. 2017;127(2):513–9.
20. Losurdo A, Dittoni S, Testani E, et al. Sleep disordered breathing in children and adolescents with Chiari malformation type I. J Clin Sleep Med. 2013;9(4):371–7.
21. Mottolese C, Szathmari A, Simon E, Rousselle C, Ricci-Franchi AC, Hermier M. Treatment of Chiari type I malformation in children: the experience of Lyon. Neurol Sci. 2011;32(suppl 3):S325–30.
22. Strahle J, Muraszko KM, Kapurch J, Bapuraj JR, Garton HJ, Maher CO. Natural history of Chiari malformation type I following decision for conservative treatment. J Neurosurg Pediatr. 2011;8(2):214–21.
23. Gagnadoux F, Meslier N, Svab I, Menei P, Racineux JL. Sleep disordered breathing in patients with Chiari malformation: improvement after surgery. Neurology. 2006;66(1):136–8.
24. Spence J, Pasterkamp H, McDonald PJ. Isolated central sleep apnea in type I Chiari malformation: improvement after surgery. Pediatr Pulmonol. 2010;45(11):1141–4.
25. Zolty P, Sanders MH, Pollack IF. Chiari malformation and sleep disordered breathing: a review of diagnostic and management issues. Sleep. 2000;23(5):637–43.

Chapter 21
Sleep Breathing Disorders in Duchenne Muscular Dystrophy

Pnina Weiss

Case

An 18-year-old male with Duchenne muscular dystrophy (DMD) was admitted because of shortness of breath, cough, and a 20-lb weight loss over 4 months. He was diagnosed at age 5 years and became non-ambulatory at 10 years. At 13 years old, he developed cardiomyopathy and was put on enalapril and carvedilol; an implantable cardioverter defibrillator was placed. At 14 years of age, he underwent polysomnography (Figs. 21.1, 21.2, and Table 21.1) which documented obstructive sleep apnea (OSA); titration with bilevel positive airway pressure with spontaneous and timed mode (BPAP S/T) demonstrated optimal treatment with 12/4 cmH_2O and backup rate 20 breaths/min, which he used with variable adherence. His pulmonary function testing is shown in Table 21.2.

Two months prior to admission, he developed cough. He was diagnosed with bronchitis and given an antibiotic. He restarted airway clearance. He had nausea, decreased appetite, and abdominal pain. He stopped using his BPAP because of chest congestion and his oral medications because of nausea. He was seen in clinic; on exam he was uncomfortable, respiratory rate 28 breaths/min, heart rate 98 beats/min, blood pressure 72/45 mmHg, pulse oximetry (SpO_2) 92% on room air, and weight 62 kg. His exam was remarkable for coarse breath sounds. A chest radiograph is shown in Fig. 21.3. Arterial blood gas on room air showed pH 7.34, PCO_2 48 mmHg, PO_2 58 mmHg, and bicarbonate 28 meq/L. Cardiac echo demonstrated moderate dilation of the left ventricle with ejection fraction 18%

P. Weiss (✉)
Department of Pediatrics, Section of Respiratory, Allergy-Immunology and Sleep Medicine, Yale School of Medicine, New Haven, CT, USA
e-mail: pnina.weiss@yale.edu

C. Won (ed.), *Complex Sleep Breathing Disorders*,
https://doi.org/10.1007/978-3-030-57942-5_21

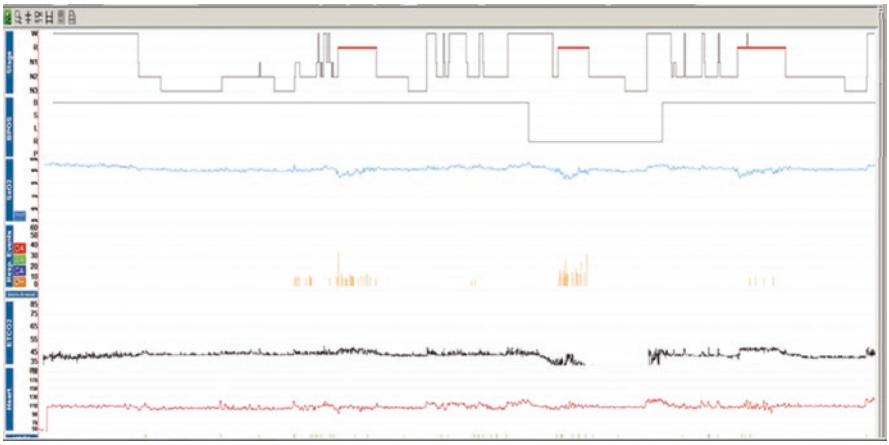


Fig. 21.1 Hypnogram of patient's PSG at age 14 years demonstrating OSA with hypoxemia during REM sleep. *PSG* polysomnography; *OSA* obstructive sleep apnea; *REM* rapid eye movement; *Stage* sleep stage (*W* wake, *R* REM, *N1* non-REM stage 1, *N2* non-REM stage 2, *N3* non-REM stage 3); *BPOS* body position (*B* back, *L* left, *R* right, *P* prone); SaO_2 arterial oxygen saturation via pulse oximetry; *Resp Events* (*OA* obstructive apnea, *MA* mixed apnea, *CA* central apnea, *OH* obstructive hypopnea); $ETCO_2$ end-tidal carbon dioxide; *Heart* heart rate

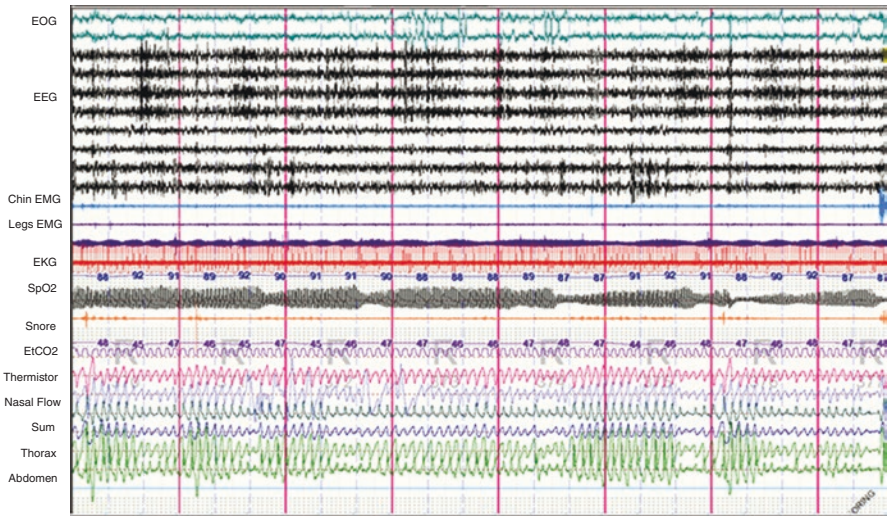


Fig. 21.2 Hypopneas with oxyhemoglobin desaturations and paradoxical respiratory effort during REM (4 min epoch) at age 14 years. *EOG* electrooculogram, *EEG* electroencephalogram, *EMG* eletromyogram, *EKG* electrocardiogram, SpO_2 pulse oximetry oxygen saturation, $EtCO_2$ end-tidal CO_2

Table 21.1 Polysomnographic report of this patient at age 14 years

TST (h)	6.2
Sleep efficiency (%)	76
Stage N1 (% TST)	4
Stage N2 (% TST)	55
Stage N3 (% TST)	23
Stage REM (% TST)	18
Obstructive AI (N/h)	0.2
REM obstructive AI (N/h)	0.9
AHI (N/h)	9.4
REM AHI (N/h)	39
Average SpO_2 awake (%)	96
Average SpO_2 asleep (%)	92
Nadir SpO_2 asleep (%)	84
Percentage time spent $SpO_2 < 90\%$ (% TST)	12
$EtCO_2$ awake (mmHg)	44
$EtCO_2$ asleep average (mmHg)	44
$EtCO_2$ asleep max (mmHg)	50
$EtCO_2 > 50$ mmHg (% TST)	0

TST total sleep time; *N1, N2, N3* Non-rapid eye movement sleep stages 1, 2, 3, respectively; *REM* rapid eye movement sleep; *AI* apnea index; *SpO_2* pulse oximetry oxygen saturation; *AHI* apnea-hypopnea index; *N* number; *$EtCO_2$* end-tidal carbon dioxide; *mmHg* millimeters of mercury

Table 21.2 Serial spirometric measurements on this patient

	3 years prior	3 months prior	This visit
FEV1 (% predicted)	29	16	15
FVC (L)	1.15	0.80	0.77
FVC (% predicted)	31	16	16
Peak cough flow (L/min)	130	120	80
MIP (cmH_2O)	−55	−45	−35
MIP (% predicted)	55	37	29
MEP (cmH_2O)	44	32	21
MEP (% predicted)	36	19	13

FEV1 forced expiration volume at 1 s, *FVC* forced vital capacity, *L* liters, *MIP* maximal inspiratory pressure, *MEP* maximal expiratory pressure

(decreased from his previous of 25% 3 months prior). He received intravenous fluid and was placed on supplemental oxygen. He became somnolent. His follow-up arterial blood gas on supplemental oxygen showed pH 7.13, PCO_2 78 mmHg, PO_2 120 mmHg, and bicarbonate 30 meq/L. He was put on BPAP S/T 12/4 cmH_2O with rate 20 breaths/min and 40% fraction of inspired oxygen (FiO_2). An arterial line was placed; follow-up arterial blood gas showed pH 7.40, PCO_2 41 mmHg,

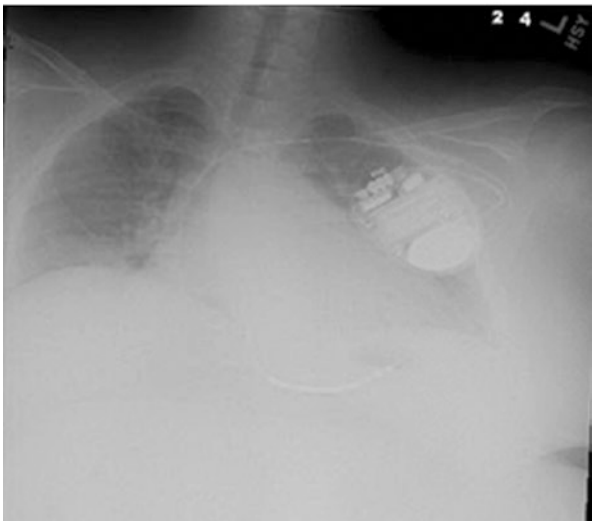


Fig. 21.3 Chest radiograph of the patient in the vignette

and PO_2 140 mmHg. He did well on BPAP S/T until he fell asleep, when he developed hypoxemia. Tidal volumes ranged 225–350 mL. Arterial blood gases showed worsening hypercapnia, which improved with increase in inspiratory positive airway pressure (IPAP) to 16 cmH_2O. Two nights later, he underwent polysomnography (PSG) which demonstrated optimal titration with average volume-assured pressure support IPAP 14–18 cmH_2O, expiratory positive airway pressure (EPAP) 4–6 cm H_2O, backup respiratory rate 22 breaths/min, and tidal volume 500 mL. He was discharged home after further stabilization of his cardiac medication regimen.

Discussion

This young adult has Duchenne muscular dystrophy with nocturnal hypoventilation and cardiomyopathy with congestive heart failure. DMD is an X-linked recessive disease affecting between 5600 and 7700 males in the United States, associated with mutations in the dystrophin gene [1, 2]. Dystrophin plays an important role in the stabilization of muscle fibers, and its loss results in degeneration of muscle fibers and muscle weakness. The onset of muscle weakness usually occurs between 2 and 3 years of age, first affecting proximal limb muscles and lower extremities. Children usually become non-ambulatory by age 12 years, as in the child in the vignette. Progressive respiratory muscle weakness resulting in respiratory failure and cardiomyopathy are the major causes of morbidity and mortality in these patients [1]. Mean survival was traditionally in late teenage years. However, mechanical ventilation, aggressive airway clearance, and glucocorticoid therapy have increased survival into the third decade [3].

Respiratory muscle weakness involving the chest wall and diaphragm results in restrictive lung disease with respiratory muscle fatigue, difficulty with airway clearance, mucus plugging, atelectasis, pneumonia, and respiratory failure. Management includes frequent monitoring of pulmonary function, lung volume recruitment, manual and mechanically assisted coughing, and nocturnal noninvasive ventilation (NIV), when indicated, with potential progression to daytime ventilation. These therapies decrease respiratory complications and improve quality of life and survival [4].

Sleep disordered breathing (SDB) is common in patients with DMD, usually progressing through four stages [5]:

- OSA without hypercapnia
- Hypoventilation, obstructive and/or central sleep apnea with hypoxemia, and/or hypercapnia during rapid eye movement (REM) sleep
- Hypoventilation, obstructive and/or central sleep apnea with hypoxemia, and/or hypercapnia during REM and non-rapid eye movement (NREM) sleep
- Daytime chronic respiratory failure

Polysomnographic evaluation with carbon dioxide (CO_2) level monitoring in children with DMD is necessary for early identification of SDB. OSA is the most common type of SDB, occurring in approximately 64% of patients and is correlated with increased body mass index (BMI) and corticosteroid use [5]. Children with DMD have increased upper airway resistance because of hypotonia of the upper airway, macroglossia, and a lower pulmonary functional residual capacity. Respiratory impairment is worse during REM sleep because during this stage of sleep, accessory respiratory muscles are paralyzed and the diaphragm becomes the primary functioning respiratory muscle. Meanwhile, the cephalad displacement of the diaphragm while recumbent reduces tidal volumes and ventilation. Children with DMD eventually develop diaphragmatic weakness associated with REM-related hypoxemia, which often worsens as pulmonary function deteriorates. REM latency has been noted to be longer in children with DMD and SDB, which may be due to sleep fragmentation from underlying SDB, or a compensatory mechanism to avoid REM sleep [6].

Hypoventilation can occur either with OSA or in isolation in children with DMD, particularly as the disease progresses. Hypoventilation in children is defined on PSG as >25% of the total sleep time with $CO_2 > 50$ mmHg. Nocturnal hypoventilation may result from an increased arousal threshold or a decrease in alveolar ventilation, respiratory muscle activity, ventilatory drive, pulmonary function, or a combination.

Central sleep apnea in association with OSA has also been reported, occurring primarily in older children with worse pulmonary function and more severe OSA [5]. Potential causes of central sleep apnea include hypoventilation, reduced hypoxic or hypercapnic ventilatory response, or increased loop gain and sleep stage instability. Cheyne-Stokes respiration has been described in patients with DMD and congestive cardiomyopathy [7]. Of note, chronic hypercapnia may actually attenuate the instability in breathing associated with cardiomyopathy by reducing the

controller gain and increasing the difference between the apneic threshold and the PCO_2. It is important to differentiate hypo- or normocapnic central events from hypercapnic central apneas that result from neuromuscular disease and respiratory muscle weakness [8]. Hypercapnic central apneas often occur during phasic REM, especially in the presence of diaphragm muscle weakness, with loss of excursion of both chest and abdominal signals.

Pulmonary function should be measured serially, starting at age 5–6 years. The best established measurements include forced vital capacity (FVC), forced expiration volume at 1 second (FEV1), peak expiratory flow rate (PEFR), and maximal inspiratory and expiratory pressures (MIP and MEP, respectively) [9]. In children with DMD, there is a maturational increase in FVC that reaches a peak (at the point at which their neuromuscular disease renders them non-ambulatory), plateaus, and then historically declines at a rate that was inversely proportional to the peak. Long-term corticosteroid therapy preserves pulmonary function, delaying the age at which the plateau in FVC occurs [10]. PSG with capnography should be considered in children with symptoms of SDB, especially because weight gain associated with glucocorticoid therapy may be a risk factor. In children who are unable to cooperate with spirometry, PSG may be considered to assess lung function.

An increase in respiratory support usually is necessary when children become non-ambulatory. Seated FVC, MIP, MEP, peak cough flow, and oxygen saturation should be measured at least every 6 months. Lung volume recruitment maneuvers are recommended when FVC decreases to 60% predicted or less, which can be performed with a self-inflated manual ventilation bag or mechanical insufflation-exsufflation device. Progressive scoliosis may require surgical intervention; guidelines addressing perioperative management have been published [11]. Preoperative PSG may be considered as an assessment of pulmonary function, if patients cannot cooperate with spirometry testing.

Further progression of disease is associated with weak cough, increasing the risk of complications such as atelectasis, aspiration, pneumonia, ventilation-perfusion mismatch, and respiratory failure, particularly during lower respiratory tract infections. Manual and mechanically assisted coughing should be initiated [4] when:

- FVC < 50% predicted
- Peak cough flow < 270 L/min
- MEP < 60 cm H_2O

For those who require assisted coughing, a home pulse oximeter is recommended.

Nocturnal assisted ventilation, preferably noninvasive, should be initiated as soon as there are symptoms of hypoventilation or SDB (e.g., fatigue, dyspnea, headaches, nocturnal awakenings, excessive daytime sleepiness, difficulty concentrating, frequent nightmares), regardless of pulmonary function. Because many children with DMD do not demonstrate symptoms of SDB, additional indications for nocturnal NIV include:

- FVC < 50% predicted
- MIP < 60 cm H_2O
- Awake SpO_2 < 95%
- Awake PCO_2 > 45 mmHg
- Abnormal sleep study

Nocturnal ventilation is also recommended for patients with abnormal sleep studies, which may include overnight oximetry, oximetry-capnography, or PSG with capnography. Sleep studies should be performed annually in those with symptoms of sleep disordered breathing since disease is progressive. Indications for nocturnal NIV based on PSG include:

- End-tidal CO_2 ($EtCO_2$) or transcutaneous CO_2 ($TcCO_2$) > 50 mmHg for >2% of the total sleep time
- Sleep-related increase in $EtCO_2$ or $TcCO_2$ > 10 mmHg over the awake baseline for >2% of total sleep time
- SpO_2 < 88% for >2% of total sleep time or for >5 min continuously
- Apnea-hypopnea index (AHI) > 5/h

Noninvasive ventilation with a backup respiratory rate, rather than continuous positive airway pressure, is preferred. A backup rate is often important as patients with DMD may have difficulty triggering breaths, particularly during REM sleep and/or as the disease worsens. Other strategies to assist with comfort and synchrony in neuromuscular disease include increasing the trigger and the cycle sensitivities, in order to allow the patient with weak respiratory effort to trigger and terminate assisted breaths appropriately. A prolonged inspiratory phase time with pressure support may be beneficial since these patients have issues with atelectasis and hypoxemia (in contrast to COPD patients on NIV, for example, who require long expiratory time to avoid air trapping). In the same manner, ventilator settings with higher peak flow and longer inspiratory time (Ti) may help optimize lung mechanics and provide a more comfortable ventilator experience for DMD patients.

The patient in the vignette met multiple criteria for initiation of NIV including decreased FVC, MEP, and peak cough along with abnormal PSG indices (SpO_2 and AHI); he was appropriately started on BPAP S/T. Serial PSG studies are recommended to follow respiratory support as overnight oximetry is not adequate to determine the adequacy of ventilation [12]. Unfortunately, the child in this vignette did not undergo subsequent PSGs until his admission. While he acutely required an increase in his ventilatory support because of pulmonary exacerbation with increasing atelectasis and congestive heart failure, he most likely needed a chronic increase in his IPAP and EPAP in order to treat his progressive restrictive disease.

Daytime NIV is indicated when, despite nocturnal NIV, a patient with DMD demonstrates:

- Awake SpO_2 < 95%
- Awake PCO_2 > 45 mmHg
- Dyspnea while awake

Noninvasive ventilation may be required during acute pulmonary exacerbations in patients with DMD. Hypoxemia is often due to hypoventilation or atelectasis; therefore, supplemental oxygen alone (as was used in this patient) often does not suffice and in some instances may worsen respiratory failure by blunting hypoxemic ventilatory response. BPAP S/T is often initially used in chronic hypercapnic respiratory failure. When disease is progressive, the best NIV modality may be volume-assured pressure support ventilation via a respiratory assist device (e.g., AVAPS™, iVAPS™) or via home ventilator (e.g., Trilogy™, LTV®). When patients lose the ability to use their upper extremities to self-apply or remove the mask interface, a ventilator (over a respiratory assist device) is recommended for its alarm and backup battery features.

Noninvasive ventilation in patients with DMD is associated with improved survival, gas exchange and sleep, and a reduction in hospitalizations, including to intensive care units [13, 14]. However, NIV does present some challenges. In children, chronic use can cause facial and nasal bridge flattening. If not carefully adjusted, patients may become dyssynchronous with their device (e.g., ineffective triggering, auto-triggering, and glottic closure) which can increase arousals, impair sleep quality, and result in decreased adherence. It is important in patients with neuromuscular disease, to ensure that the patient can effectively trigger ventilation. As previously mentioned, trigger/cycle sensitivities, peak flow, and inspiratory time should be carefully adjusted for patient comfort.

The potential adverse effects of using NIV in the context of cardiomyopathy with decreased ejection fraction merit consideration. Cardiomyopathy, with ensuing heart failure and arrhythmias, has emerged as a major determinant of survival in patients with DMD [15]. Early and consistent cardiac evaluation is recommended, especially in the late, non-ambulatory stage. Symptoms of heart failure may be difficult to detect in non-ambulatory patients with DMD. Fatigue, weight loss, vomiting, and abdominal pain may indicate worsening cardiac function, as was the case in the patient in the vignette. First-line therapy includes angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, which are often initiated even in asymptomatic patients with DMD as early as age 10 years [4]. Beta-adrenergic blockers are usually second-line therapy [16]. In an early randomized study of patients with DMD, NIV was instituted when FVC decreased below 50%; when compared to controls, there was quadruple the mortality rate in the treated group [17]. However, the study was later criticized as there was a higher prevalence of left ventricular dysfunction in those on NIV. So, while there is a potential for NIV to decrease cardiac output in patients with left ventricular dysfunction (by increasing intrathoracic pressure and decreasing left ventricular preload), at present, its use is not contraindicated in those who require it for respiratory support, especially if they are given cardioprotective medications. The argument for using NIV in patients with cardiomyopathy is that it has been shown to improve survival. It may be that with the potential adverse effects of respiratory insufficiency on cardiac function, earlier institution of NIV could have a cardioprotective effect [16].

It should also be noted that cardiomyopathy and heart failure in DMD has been associated with central sleep apnea with Cheyne-Stokes respiration. NIV

(especially without a backup rate) may exacerbate Cheyne-Stokes breathing by over-ventilating the patient and worsening loop gain. CSA related to Cheyne-Stokes breathing is often a hypocapnic phenomenon and occurs almost exclusively during NREM sleep, due to the dependence on PCO_2 and PO_2 on ventilatory control during this sleep stage. In contrast, CSA associated with neuromuscular disease has a very different pattern and mechanism from that seen with heart failure. Neuromuscular disease results in a hypercapnic central sleep apnea phenotype. In this case, central hypopneas and apneas emerge typically during REM sleep when respiratory muscle strength is at its weakest. For this type of central sleep apnea, NIV is the treatment of choice. Therefore, in a DMD patient with cardiomyopathy and CSA, careful attention has to be made at phenotyping the SDB (i.e., determine if it is hypocapnic CSA (driven by the cardiomyopathy) or hypercapnic CSA (driven by respiratory muscle weakness)). Treatment will differ depending on the CSA type, and the wrong therapy may actually worsen the sleep breathing disorder. Adaptive servo-ventilation (ASV) would be contraindicated in DMD patients because of both cardiomyopathy and neuromuscular disease.

Clinical Pearls

- Progressive respiratory muscle weakness resulting in respiratory failure and cardiomyopathy are major causes of morbidity and mortality in patients with Duchenne muscular dystrophy (DMD).
- Sleep disordered breathing in the form of OSA, hypoventilation, and CSA with and without Cheyne-Stokes respiration can be seen.
- OSA is the most common SDB, occurring in 64% of children treated with corticosteroids. Risk factors for OSA in patients with DMD include upper airway hypotonia, macroglossia, restrictive pulmonary disease, diaphragm muscle weakness, and obesity.
- Hypoventilation occurs due to respiratory muscle weakness. Patients may require noninvasive ventilation during sleep and, if severe, during the daytime. Special attention to features such as inspiratory time, flow rate, trigger, and cycle sensitivity should be made to optimize positive airway pressure or ventilator synchrony in DMD patients who may otherwise have difficulty triggering breaths or become dyssynchronous with the machine. In addition, a backup respiratory rate is always recommended due to this concern of poor breath triggering.
- Central sleep apnea with and without Cheyne-Stokes respiration can be seen in patients with DMD with cardiomyopathy. It is important to distinguish whether CSA is related to hypoventilation or high loop gain and heart failure, since each may be treated differently.
- Noninvasive ventilation in patients with DMD is associated with improved survival, gas exchange and sleep, and a reduction in hospitalizations, including to intensive care units. NIV is recommended in patients with DMD who require ventilatory support even in the presence of cardiomyopathy with low ejection fraction.

References

1. Finder J, Mayer OH, Sheehan D, Sawnani H, Abresch RT, Benditt J, Birnkrant DJ, Duong T, Henricson E, Kinnett K, McDonald CM, Connolly AM. Pulmonary endpoints in Duchenne muscular dystrophy. A workshop summary. Am J Respir Crit Care Med. 2017;196(4):512–9.
2. Nowak KJ, Davies KE. Duchenne muscular dystrophy and dystrophin: pathogenesis and opportunities for treatment. EMBO Rep. 2004;5(9):872–6.
3. Schram G, Fournier A, Leduc H, Dahdah N, Therien J, Vanasse M, Khairy P. All-cause mortality and cardiovascular outcomes with prophylactic steroid therapy in Duchenne muscular dystrophy. J Am Coll Cardiol. 2013;61(9):948–54.
4. Birnkrant DJ, Bushby K, Bann CM, Alman BA, Apkon SD, Blackwell A, Case LE, Cripe L, Hadjiyannakis S, Olson AK, Sheehan DW, Bolen J, Weber DR, Ward LM, Group DMDCCW. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. Lancet Neurol. 2018;17(4):347–61.
5. Sawnani H, Thampratankul L, Szczesniak RD, Fenchel MC, Simakajornboon N. Sleep disordered breathing in young boys with Duchenne muscular dystrophy. J Pediatr. 2015;166(3):640–645 e641.
6. Nozoe KT, Moreira GA, Tolino JR, Pradella-Hallinan M, Tufik S, Andersen ML. The sleep characteristics in symptomatic patients with Duchenne muscular dystrophy. Sleep Breath. 2015;19(3):1051–6.
7. Lemay J, Series F, Senechal M, Maranda B, Maltais F. Unusual respiratory manifestations in two young adults with Duchenne muscular dystrophy. Can Respir J. 2012;19(1):37–40.
8. Aboussouan LS, Mireles-Cabodevila E. Sleep-disordered breathing in neuromuscular disease: diagnostic and therapeutic challenges. Chest. 2017;152(4):880–92.
9. Meier T, Rummey C, Leinonen M, Spagnolo P, Mayer OH, Buyse GM, Group DS. Characterization of pulmonary function in 10-18 year old patients with Duchenne muscular dystrophy. Neuromuscul Disord. 2017;27(4):307–14.
10. Moxley RT 3rd, Pandya S, Ciafaloni E, Fox DJ, Campbell K. Change in natural history of Duchenne muscular dystrophy with long-term corticosteroid treatment: implications for management. J Child Neurol. 2010;25(9):1116–29.
11. Hull J, Aniapravan R, Chan E, Chatwin M, Forton J, Gallagher J, Gibson N, Gordon J, Hughes I, McCulloch R, Russell RR, Simonds A. British Thoracic Society guideline for respiratory management of children with neuromuscular weakness. Thorax. 2012;67(Suppl 1):i1–40.
12. Paiva R, Krivec U, Aubertin G, Cohen E, Clement A, Fauroux B. Carbon dioxide monitoring during long-term noninvasive respiratory support in children. Intensive Care Med. 2009;35(6):1068–74.
13. Ishikawa Y, Miura T, Ishikawa Y, Aoyagi T, Ogata H, Hamada S, Minami R. Duchenne muscular dystrophy: survival by cardio-respiratory interventions. Neuromuscul Disord. 2011;21(1):47–51.
14. Crescimanno G, Misuraca A, Purrazzella G, Greco F, Marrone O. Subjective sleep quality in stable neuromuscular patients under non-invasive ventilation. Sleep Med. 2014;15(10):1259–63.
15. Birnkrant DJ, Ararat E, Mhanna MJ. Cardiac phenotype determines survival in Duchenne muscular dystrophy. Pediatr Pulmonol. 2016;51(1):70–6.
16. McNally EM, Kaltman JR, Benson DW, Canter CE, Cripe LH, Duan D, Finder JD, Hoffman EP, Judge DP, Kertesz N, Kinnett K, Kirsch R, Metzger JM, Pearson GD, Rafael-Fortney JA, Raman SV, Spurney CF, Targum SL, Wagner KR, Markham LW. Contemporary cardiac issues in Duchenne muscular dystrophy. Circulation. 2015;131(18):1590–8.
17. Raphael JC, Chevret S, Chastang C, Bouvet F. Randomised trial of preventive nasal ventilation in Duchenne muscular dystrophy. French multicentre cooperative group on home mechanical ventilation assistance in Duchenne de Boulogne muscular dystrophy. Lancet. 1994;343(8913):1600–4.

Index

C. Won (ed.), *Complex Sleep Breathing Disorders*,
https://doi.org/10.1007/978-3-030-57942-5