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

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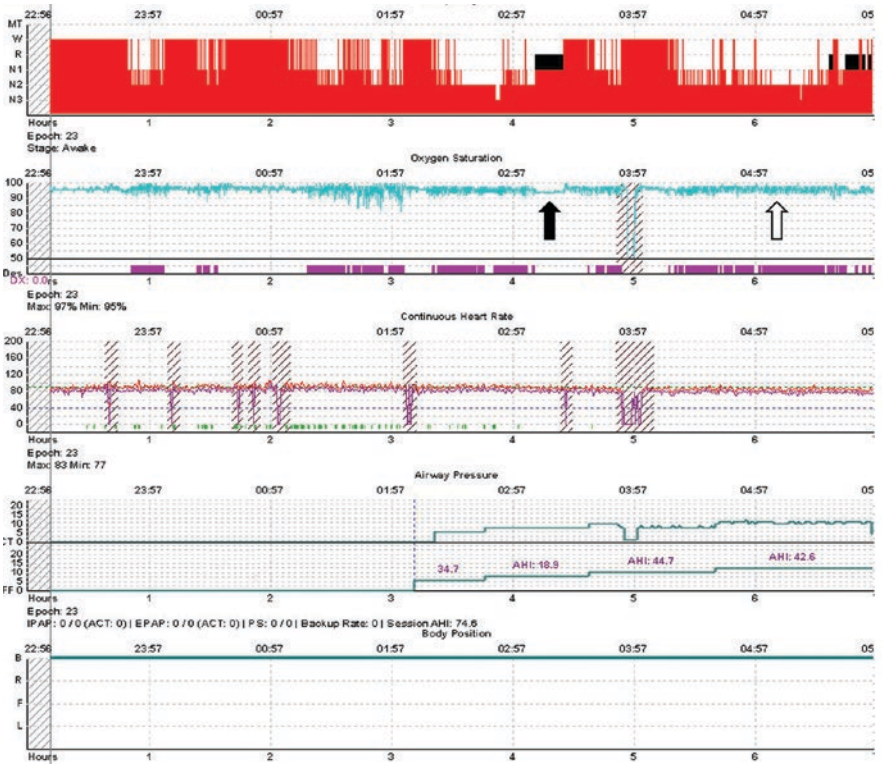

Fig. 8.1 Study hypnogram showing the patterns of treatment-emergent central sleep apnea on a split polysomnogram. Notice the non-rapid eye movement (NREM) predominance of events during application of continuous positive airway pressure and characteristic improvement in REM sleep (filled arrow). Deoxygenation 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

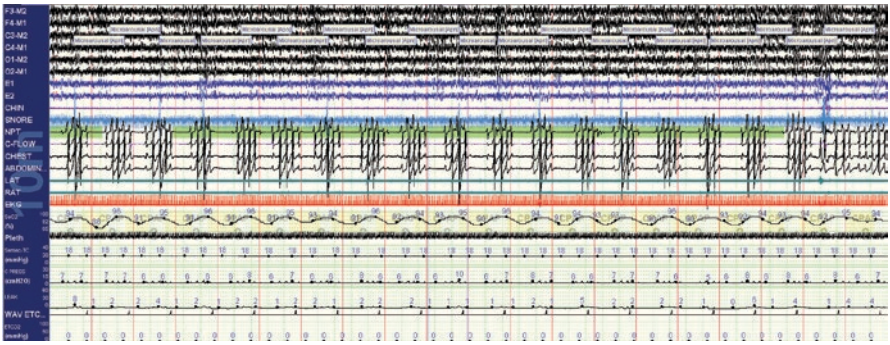

Fig. 8.2 Treatment-emergent central apneas (TE-CSA) while on continuous positive airway pressure (CPAP). Ten-minute screen compression; each vertical line is 30 s. Note the recurrent central apneas and periodic breathing with a cycle length of approximately 30 s, shorter than in those with heart failure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

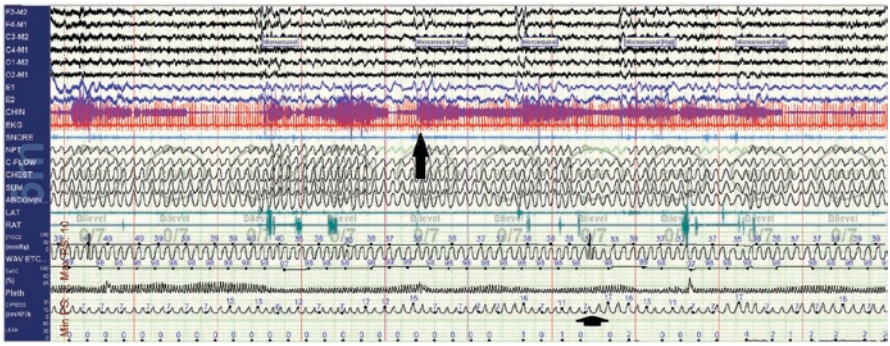

Fig. 8.3 Pressure cycling during adaptive ventilation treatment with nearly normal flow. Five-minute compression snapshot showing pressure cycling (arrow head). The C-PRESS channel is the pressure output from the adaptive ventilator. This 56-year-old man had predominantly central apneas, which were eliminated. 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].

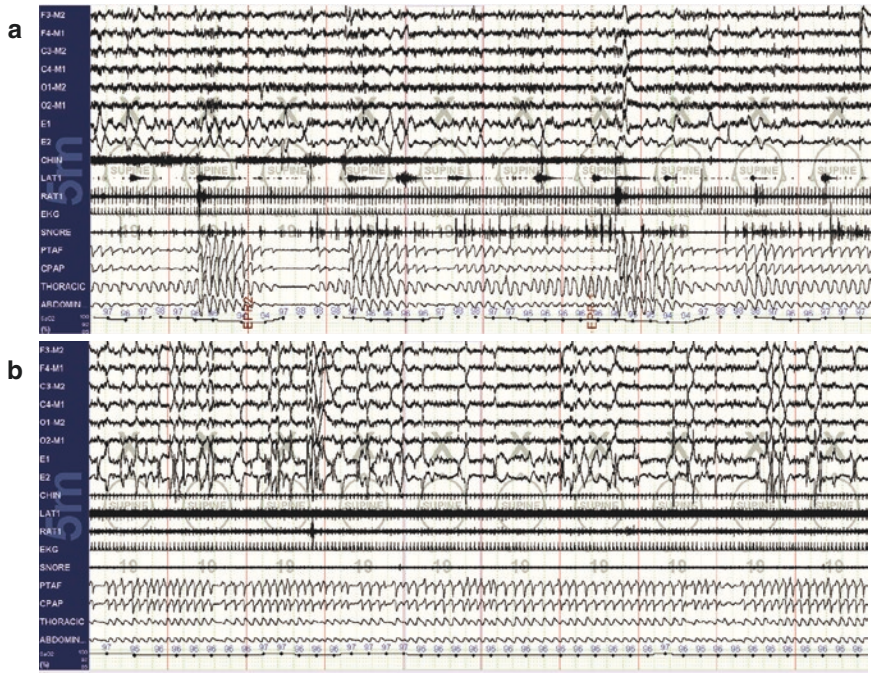

Fig. 8.4 (**a**) NREM-dominant sleep apnea, with continuous positive airway pressure (CPAP) during NREM sleep. Five-minute screen compression; each vertical line is 30 s. Unresolved respiratory events occur across a range of CPAP (5–19 cm) with long cycle events, some periodic breathing features, and 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.

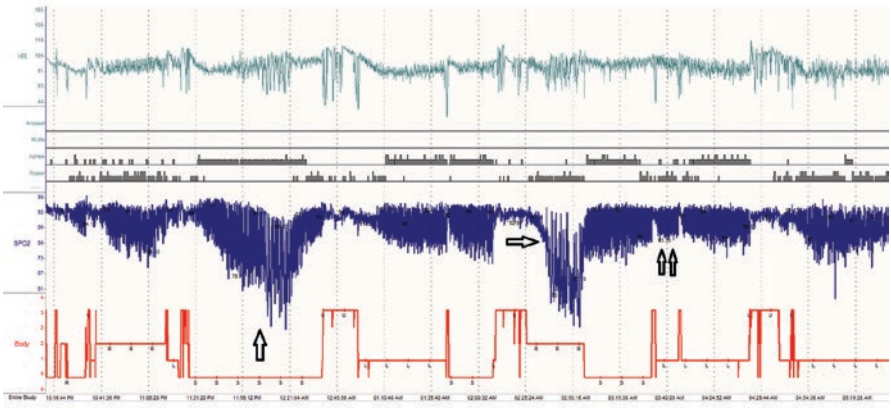

Fig. 8.5 Manifestation of different desaturation patterns on home sleep study. Single arrows represent irregular, progressive, and sometimes V-shaped contour desaturations often associated with rapid eye movement (REM) sleep and obstructive events. Double arrows highlight more smooth, symmetric, and "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].

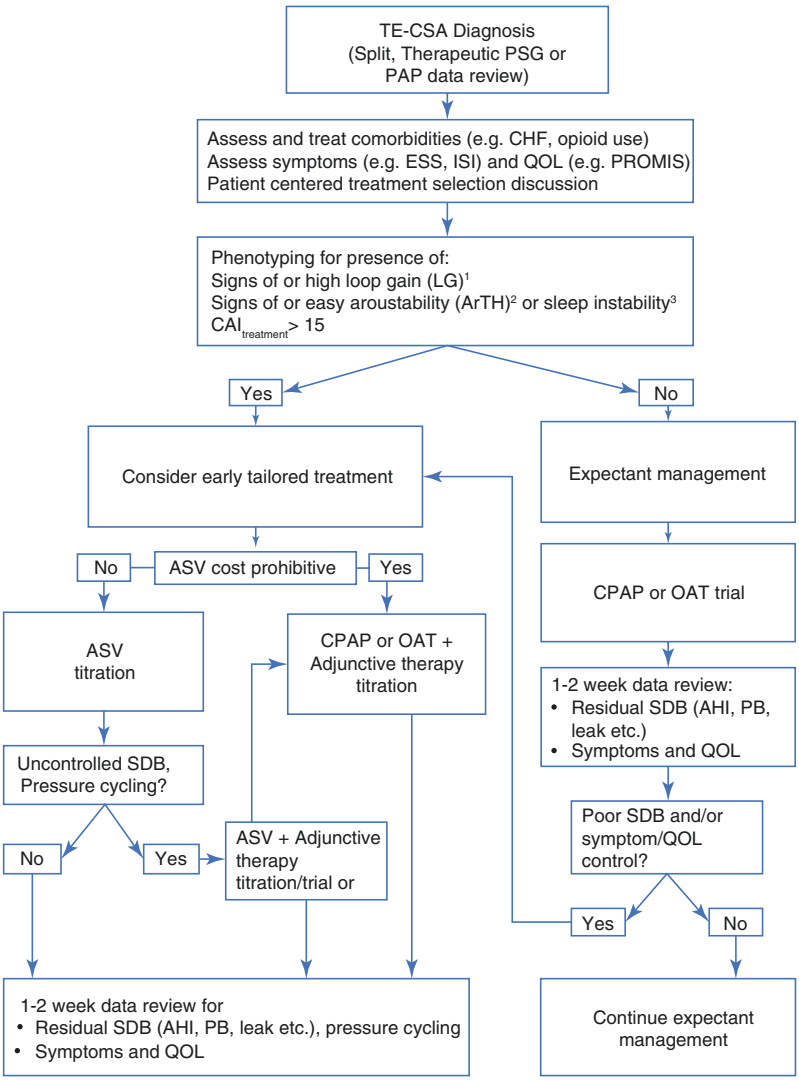

Fig. 8.6 One approach to management of TE-CSA. Adjunctive therapy targeting *high loop gain (LG)* includes acetazolamide, O_2, non-vented mask, enhanced expiratory rebreathing space; Adjunctive therapy targeting *low arousal threshold (ArTH) or fragmented sleep* includes sedative hypnotics. All patients 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.

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