

Treatment-Emergent Central Apnea

Physiologic Mechanisms informing clinical practice.

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Abbreviations: AHI (apnea-hypopnea index), TECSA (Treatment-Emergent Central Sleep Apnea), CPAP (continuous positive airway pressure), ASV (Adaptive Servo Ventilation), BPAP (Bi-level Positive Airway Pressure), OSA (obstructive sleep apnea), SDB (sleep-disordered breathing).

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ABSTRACT

The purpose of this review is to describe our management approach to patients with treatment-emergent central sleep apnea (TECSA).

The emergence of central sleep apnea during positive airway pressure therapy occurs in approximately 8% of titration studies for obstructive sleep apnea, and has been associated with several demographic, clinical and polysomnographic factors, as well as factors related to the titration study itself. TECSA shares similar pathophysiology with central sleep apnea. In fact, central and obstructive sleep apnea pathophysiologic mechanisms are inextricably intertwined, with ventilatory instability and upper airway narrowing occurring in both entities. TECSA is a “dynamic” process, with spontaneous resolution with ongoing positive airway pressure therapy in most patients, persistence in some, or appearing de novo in a minority of patients. Management strategy for TECSA aims to eliminate abnormal respiratory events, stabilize sleep architecture, and improve the underlying contributing medical comorbidities. Continuous positive airway pressure therapy remains a standard therapy for TECSA. Expectant management is appropriate given its transient nature in most cases, while select patients would benefit from an early switch to an alternative positive airway pressure modality. Other treatment options include supplemental oxygen, and pharmacologic therapy.

I. Introduction

Treatment-emergent central sleep apnea (TECSA) -previously called complex sleep apnea - refers to the development of central apnea after the initiation of positive pressure therapy for obstructive sleep apnea (OSA). The ICSD-3 diagnostic criteria for this condition include: 1) the presence of predominantly OSA on diagnostic polysomnography (PSG), 2) resolution of obstructive events with positive airway pressure (PAP) therapy without a backup rate, and 3) the emergence or persistence of central apneas or hypopneas on PAP therapy with central apnea index (CAI>5) events/hour of sleep, and the number of central events is $\geq 50\%$ of the total events.¹.

The presence of central apnea upon initiation of PAP therapy underscores the pathophysiologic overlap between OSA and CSA including instability of the ventilatory motor output, as expressed by high loop gain in patients with OSA and the occurrence of upper airway narrowing or occlusion during central apneas and hypopneas.²⁻⁴. Thus, TECSA is a “dynamic” process, with spontaneous resolution with ongoing PAP therapy in most patients, persistence in some, or appearing de novo in a minority of patients.⁵⁻⁸ The AASM practice parameters for treatment of CSA syndromes in adults did not specifically address TECSA. More recently, TECSA has been briefly included in a European Respiratory Society Task Force document on nocturnal central breathing disturbances. Therefore, TECSA treatment remains a gray area as caution is mandated when therapeutic approach is extrapolated from other forms of central apnea.

In this review, we will describe common clinical scenarios where TECSA is encountered, discuss our management approach in the context of current guidelines and the relevant literature, and present our approach to the treatment of TECSA in the clinical setting.

II. Case Scenarios

Case # 1

A 53-year-old healthy male referred in consultation for evaluation of snoring and hypersomnia. PSG revealed OSA with an apnea-hypopnea index (AHI) of 56/hr. Auto-PAP was prescribed at 5 to 15 cm H₂O. Wireless monitoring data during a follow-up visit at 4 weeks of therapy revealed full PAP adherence. Residual AHI was elevated at 23/hr due to the emergence of central events. The patient was asymptomatic and sleeping well.

Case # 2

An obese, but otherwise healthy 28-year-old male was referred in consultation after being involved in a motor vehicle accident when he fell asleep while driving. A split-night PSG revealed mostly obstructive respiratory events with an AHI of 42.6 events/hr. CPAP therapy was titrated to 14 cm H₂O. Obstructive apneas and hypopneas were eliminated at CPAP of 12 cm H₂O. Central apneas appeared at CPAP of 8 cm H₂O and were reduced but not eliminated at CPAP of 14 cm H₂O. Wireless monitoring data after 2 weeks of therapy at CPAP of 14 cm H₂O revealed a suboptimal adherence of 48.5% use > 4hrs and a residual AHI of 17.4/hr mainly due to central apneas. The patient complained of PAP intolerance and significant sleep fragmentation.

III. Review of current literature

A. Determinants of breathing instability during sleep: Lessons from physiologic studies

Respiration during NREM sleep is critically dependent on P_aCO₂; the susceptibility to central apnea manifests by unmasking the hypocapnic apneic threshold.⁹ Interestingly, central apnea rarely occurs as a single event; instead, it occurs in cycles of apneas or hypopneas, alternating with hyperpnea, a reflection of the negative feedback closed-loop cycle that characterizes ventilatory control. This is often described using the engineering concept of “loop gain”¹⁰

combining mainly two factors including: 1) chemoreflex sensitivity, (controller gain) reflecting the response of the ventilatory system to changing $P_{ET}CO_2$, (the controller), and 2) the effectiveness of the lung/respiratory system in lowering $P_{ET}CO_2$ in response to hyperventilation (the plant). The overall loop gain is the multiplicative result of several distinct and interactive mechanisms (chemosensitivity, plant gain, and circulatory delay).¹⁰

The “loop gain” is a valuable construct to understand the contribution of breathing instability to the pathogenesis of sleep-disordered breathing (SDB), especially Cheyne-Stokes respiration. However, SDB includes a multitude of physiologic derangements that defy the assumed rhythmic periodicity of loop gain including high peripheral chemoreflex gain,¹¹ frequent transient arousals from sleep, and abnormal cerebrovascular responsiveness,¹² factors that promote further breathing instability during sleep.

The propensity to develop central apnea during sleep could be determined experimentally by inducing central apnea using nasal mechanical ventilation.¹³ The requisite magnitude hypocapnia to induce central apnea is referred to as the CO_2 reserve. A narrow reserve CO_2 indicate a high propensity to develop central apnea and vice versa. This experimental paradigm also allows for determination of the plant gain and chemoreflex sensitivity (controller gain).

Findings from experimental studies of induced central apnea have provided significant insight regarding the determinants of CSA and may inform our understanding of TECSA, as well as potential therapeutic approaches. For example, increased controller gain may explain increased propensity to central apnea in men versus pre-menopausal women,¹⁴ and in older adults compared to young and middle-aged adults.¹⁵ Likewise, patients with OSA also demonstrate higher propensity to induced central apnea, and higher loop gain, compared to healthy matched adults.¹³ Interestingly, PAP therapy for 4 weeks is associated with decreased controller gain and

widening of the CO₂ reserve.¹³ This observation may provide the physiologic explanation for the noted resolution of TECSA in many patients following PAP therapy for 3 months.

Plasticity is a fundamental property of the ventilatory control system. Controller gain/chemoreflex sensitivity displays substantial plasticity in response to physiologic interventions or pharmacologic manipulations. For example, acute intermittent hypoxia, mimicking recurrent respiratory events on oxygenation, results in increased controller gain and subsequent narrowing of the CO₂ reserve.¹⁶ In contrast, administration of a hyperoxic gas mixture results in decreased controller gain and widening of the CO₂ reserve.¹⁷ Finally, manipulation of male sex hormones exerts a predictable effect on the controller gain and the CO₂ reserve. Specifically, administration of testosterone¹⁸ to premenopausal women was associated with increased hypocapnic chemoreflex sensitivity (controller gain), whereas administration of leuprolide¹⁹ or finasteride²⁰ to young men exerts the opposite effect. The mutability of the controller gain can be utilized therapeutically in the treatment of central apnea including TECSA.

The propensity to central apnea is also influenced by the changes in the background drive to breathe. Increased ventilatory drive and ensuring low alveolar pressure of CO₂ (PaCO₂), for a given metabolic rate, promotes stability by decreasing the magnitude of hypocapnia for a given change in alveolar ventilation, whereas reduced drive and elevated PaCO₂ increases the magnitude of hypocapnia for a given change in alveolar ventilation. For example, background hypoventilation, which may occur in response to opioid analgesics, increases the propensity to develop central apnea. In contrast, administration of acetazolamide is associated with decreased plant gain and mitigation of the risk for central apnea.²¹

Central apnea may also influence the development of OSA. Patients with unfavorable upper airway anatomy are dependent on ventilatory motor output to preserve upper airway patency.

Studies using upper airway imaging have shown that central apnea ² and hypopnea ⁴ result in pharyngeal narrowing or occlusion in normal individuals and SDB patients. Pharyngeal closure combined with mucosal and gravitational factors may impede pharyngeal opening and necessitate a substantial increase in a drive that perpetuates breathing instability. Thus, investigating determinants of central apnea may be relevant to understanding the pathogenesis of upper airway obstruction in susceptible individuals.

B. Prevalence and risk factors

The prevalence of TECSA is uncertain given the variability in applying the diagnostic criteria. A systematic review estimated a prevalence of 8% (range 5% to-20%). ²² One limitation is the identification and classification of hypopnea on PSG in most clinical sleep laboratories under “obstructive” events, given the limited value of precise classification in terms of management decisions. Therefore, pre-PAP central SDB cannot be excluded in a substantial proportion of patients seen in clinical practice. TECSA risk factors are summarized in Table 1.

C. Natural history: Spontaneous resolution vs. persistence

TECSA is a dynamic condition that appears to resolve after several weeks of PAP therapy, ⁶⁻⁸ with a spontaneous resolution rate between 54% - 86 %. ²³ One caveat is the tendency to aggregate PAP-persistent CSA and PAP-emergent CSA under the rubric TECSA. While the occurrence of TECSA may implicate PAP or the relief of upper airway obstruction as the “triggers”, persistent CSA –after a period of PAP therapy- may indicate PAP failure and the need for an alternative treatment of CSA. A recent study used PAP telemonitoring to assess CSA trajectories during PAP therapy at weeks 1 and 13 after initiating therapy in a large number of patients (n=133,006).⁸ Overall, TECSA was noted in 3.5% of the patients, resolved in over a half, persisted in about a quarter of affected patients, and was associated with higher rate of therapy termination. Similar findings were demonstrated in a recent systematic review of 5

studies analyzing the natural evolution of TECSA (n= 135,283).²³ Of note, all studies except one allowed inclusion of patients with CSA at baseline. Patients affected by TECSA may be less adherent to therapy and are at higher risk of PAP intolerance, manifesting as dyspnea, air hunger, and involuntary CPAP mask removal during the night.^{6,24} Moreover, delayed TECSA is another distinct form of TECSA that insidiously manifests on a subsequent titration study despite the absence of TECSA on the first titration study. In summary, TECSA has a dynamic nature; being transient (weeks to months) in most patients, persistent over the long run, or delayed, appearing on a subsequent titration study after being absent on baseline assessment.

IV. Review of guidelines

The 2012 AASM CSA treatment guidelines did not specifically address TECSA.²⁵ In contrast, the European Respiratory Society 2017 guidelines defined TECSA as CSA that emerges and persists under CPAP use and excluded pre-existing CSA and transient CSA that resolves with ongoing PAP use as well as CSA in patients with underlying cardiovascular, endocrine, renal or neurological diseases.²⁶ They suggested a switch to ASV in patients with TECSA who have a residual AHI > 15/h on CPAP.

V. Management Strategy

a. Goals of Therapy

Management options for TECSA parallel those used for the treatment of CSA. In addition, several factors must be considered for appropriate management of TECSA. Table 2. is a summary of different treatment modalities and their mechanism(s) of action.

First, the overall aim of treatment of TECSA is to reduce the AHI and improve residual symptoms. However, The ICSD-3 diagnostic criteria do not include clinical features among the diagnostic criteria, and studies investigating treatment options have used the frequency of

respiratory events as the outcome variable. Thus, management strategy should be individualized based on the underlying etiology and co-morbid conditions.

Second, the appearance of TECSA on polysomnography may reflect one or more pathophysiologic mechanisms:

- Unmasking of central apnea: patients with central SDB and an unfavorable upper airway anatomy may develop pharyngeal narrowing and obstructive apneas during periods of central apnea or reduced ventilatory motor output,² such as during hypocapnic central hypopnea. Relief of upper airway obstruction with PAP therapy may unmask the underlying central apnea.
- PAP-induced events: rapid changes in PAP level or mask leak may rapidly decrease arterial PCO₂ below the hypocapnic apneic threshold, leading to central apnea.
- Effect of intermittent hypoxia: exposure to chronic intermittent hypoxia is associated with enhanced peripheral chemoreceptor activity. Likewise, acute intermittent hypoxia, as seen in OSA, is associated with increased propensity to central apnea.¹⁶

Third, the etiologic variability of TECSA may explain the variability in treatment response, as many published studies include those with PAP-refractory CSA.^{6,27} In addition, most patients with CSA have comorbid OSA.²⁸ The lack of randomized controlled studies investigating the treatment of TECSA renders estimates of treatment response and natural history imprecise.

The presence of recurrent central apnea indicates elevated loop gain via one of its two components: plant gain or controller gain. Patients with persistent TECSA may be those with the highest loop gain values.^{29,30} Stanchina et al. documented in a pilot study that calculated loop gain was higher for patients with persistent TECSA after 1 month of CPAP therapy and that loop gain measurement may facilitate determination of patients who need alternative modes of PAP therapy.³⁰ Thus, identification of the underlying abnormality may be beneficial. For instance, CPAP

could decrease plant gain by increasing lung volume, whereas elevated chemosensitivity may respond to supplemental oxygen.^{29,31} A combination of therapies may be necessary when several abnormalities exist in an individual patient, e.g. CPAP plus oxygen.

b. Proposed approach to treatment

Optimization and Watchful observation

This strategy is based on the premise that central apnea will resolve spontaneously in most patients after 2-3 months of PAP therapy.^{6,23} We favor a cautious watchful waiting approach, informed by the overall clinical picture and the severity of residual AHI. This approach requires a careful assessment of co-morbid conditions, appropriate adjustments of opioid analgesics, and optimization of medical management, especially for patients with heart failure. Telemonitoring of device transmission data may obviate the need for repeat PSG in the majority of patients. Patients should be counseled to continue CPAP use pending reassessment, while addressing mask leak or adjusting pressure level if needed.³² A combination of symptomatic improvement and low residual AHI (<15/hr) supports the continuation of CPAP therapy. Figure 1. outlines a proposed treatment algorithm that we use in our sleep center.

Bi-level therapy (BPAP or ASV)

Persistence of TECSA (AHI>15/hr) may require switching to an alternative PAP mode (ASV or BPAP with a backup rate), especially in the setting of residual symptoms. Both modes provide EPAP to eliminate OSA and an inspiratory pressure above EPAP to increase ventilation. BPAP delivers fixed IPAP and EPAP, the difference between both pressures is the magnitude of pressure support (PS). Accordingly, BPAP delivers fixed tidal volume for a given pressure support level. In contrast, ASV, which was originally introduced as a treatment for central apnea associated with heart failure, mitigates CSA by providing a variable magnitude of pressure support, above the amount of EPAP required to eliminate obstructive events, and a backup up

respiratory rate. The magnitude of the PS level is reciprocal to the observed respiratory effort over a 3-4 minutes window. In other words, ASV provides a higher PS level during low flow periods and less PS when flow is high; thus, dampening the magnitude of hyperventilation. Overall, ASV is more efficacious than CPAP or BPAP in eliminating respiratory events in patients with TECSA.^{33,34} On potential limitation of the available literature is that the majority of studies investigating ASV have been sponsored by the device manufacturers, employing proprietary algorithms, and testing intermediate physiologic outcomes rather than clinical outcomes. In a direct comparison between ASV and CPAP, Morgenthaler et al³⁵ demonstrated a higher rate of CSA resolution 90 days after initiation of ASV compared to CPAP. However, the difference of 5.5 events per hour was lower than the *a priori* determined clinically relevant difference of 10 events per hour, and there was no difference in PAP adherence or patient-reported outcomes such as Epworth Sleepiness Scale, quality of life, and feeling refreshed. To our knowledge, Morgenthaler study was the only study that compared measures of symptomatic improvement between PAP modalities, and the first to evaluate quality of life measure in patients with TECSA.

The presence of co-morbid conditions may influence the response to CPAP therapy. For example, CSA associated with heart failure may be refractory to CPAP in up to 50% of patients, even with long-term use.^{36,37} Select patients may need adequate care with early switch to alternative PAP modes.^{38,39} However, ASV is contraindicated in patients with CSA associated with heart failure and reduced ejection fraction (HFrEF), based on the findings of the SERVE-HF, a randomized trial of ASV versus standard medical therapy in patients with predominantly CSA due to HFrEF (EF \leq 45%) in which ASV was associated with a 6% absolute increase in all-cause mortality and cardiovascular mortality compared with standard medical therapy.⁴⁰

The aforementioned considerations underpin our approach to use ASV in an individualized manner. Specifically, we use ASV, in the absence of a contraindication, if symptomatic TECSA persists despite the use of CPAP, alone or with supplemental oxygen (see below).

BPAP is another option for TECSA. Nevertheless, BPAP in the spontaneous mode may worsen central apneas.^{41,42} In contrast, several studies have shown an improvement in AHI with the use of BPAP with a backup rate (BPAP in spontaneous timed mode or BPAP-ST).^{33,34,41} One peculiar observation is the delayed emergence of TECSA 6 weeks after BPAP-ST was initiated.³³ This finding would not be expected to happen with ASV given the automated pressure support adjustment to ventilatory instability. Special care must be taken to use the least magnitude of effective PS to minimize hyperventilation and the risk of re-emergence of TECSA. Furthermore, clinicians must optimize patient-ventilator synchrony to minimize arousals and sleep state instability, as this also destabilizes ventilation.

Supplemental oxygen

Oxygen therapy had been proven to reduce CAI even in the absence of associated nocturnal hypoxemia.^{43,44} Increased arterial PO_2 works by lowering carotid-body chemosensitivity, therefore buffering oscillations in ventilatory control.⁴⁵ The addition of oxygen to CPAP may result in better control of TECSA, via reduction of the hypoxic respiratory drive and increasing cerebral PCO_2 as CO_2 is displaced from hemoglobin by the increased oxygen level (Haldane effect).⁴⁶

Nocturnal home oxygen therapy (HOT) has been extensively studied in patients with CSA and CHF. The CHF-HOT study group assessed the efficacy of HOT on SDB and other variables in 56 patients with stable CHF and CSA-CSB.⁴⁷ The study demonstrated that HOT significantly reduced AHI. A recent large network meta-analysis of 14 randomized controlled trials (n=919 patients) comparing the effect of any combination of CPAP, ASV, O_2 or inactive control on AHI in patients with CHF and CSA/CSB.⁴⁸ The authors found that ASV was the most efficacious therapy, (87.8%), followed by oxygen (12.2%). Therefore, oxygen is reserved for patients who do not tolerate PAP therapy or used in combination with PAP when response to PAP alone is unsatisfactory.⁴⁹ Oxygen is also beneficial in hypoxemic patients with cardiac or pulmonary

comorbidities requiring oxygen therapy independent of their TECSA. However, reimbursement for supplemental oxygen, in the absence of sustained hypoxia, is often a barrier.

Acetazolamide

Acetazolamide (ACZ), a mild diuretic, is associated with increased ventilatory motor output by inducing metabolic acidosis. Several studies have demonstrated efficacy of acetazolamide in reducing the severity of central apnea. There is empiric evidence that administration of acetazolamide is associated with widening of the CO₂ reserve, likely attributed to decreased plant gain and controller gain.²¹ However, the effectiveness of acetazolamide after prolonged use is yet to be determined. We use acetazolamide on a case-by-case basis for in cases of persistent symptomatic TECSA as an adjunct to CPAP therapy.^{21,50,51}

Positional therapy

Several studies have noted increased central apnea frequency in the supine position, likely attributed to passive upper airway collapse during CSA, lower lung volumes, and worsened pulmonary vascular congestion and associated hypoxia. New generation sleep position devices may be efficacious as salvage therapy for patients with CSA who are intolerant to PAP therapy.⁵² We are cautious in utilizing this approach to treat TECSA pending outcome data.

VI. Case Scenarios Outcomes

The first patient had documented initial optimal adherence and reported substantial clinical improvement despite elevated residual AHI. Given the absence of TECSA risk factors and the overall favorable clinical picture, expectant management was an acceptable initial choice. Close telephone follow-up along with routine access to wireless monitoring data allowed for proper assessment of any potential symptomologic worsening as well as the time course of TESCA evolution and guided the potential need for a repeat titration study. Residual AHI at 3 months was 14/hr. The patient remained asymptomatic. No further action was taken.

The second patient failed expectant management given significant discomfort with therapy and persistence of TECSA (residual AHI>15 events/hr). An ASV titration study was ordered and ASV was successful in eliminating both obstructive and central respiratory events. At 4 weeks follow up, patient had significantly improved adherence to therapy with 76% use >4 hrs and reported “quiet restful sleep”. PAP download data confirmed the absence of TECSA.

VII. Summary points

- TECSA is a complex process that combines central breathing instability and unfavorable upper airway structure and function.
- TECSA is a “dynamic process” with spontaneous resolution with ongoing PAP therapy in most patients (transient TECSA), persistence in some (persistent TECSA), or appearing de novo in a minority of patients (delayed TECSA).
- Expectant management is appropriate in asymptomatic patients with close follow-up.
- Switch to alternate PAP modalities (ASV, BPAP-ST) is appropriate in symptomatic patients, and when AHI>15/hr on follow-up.

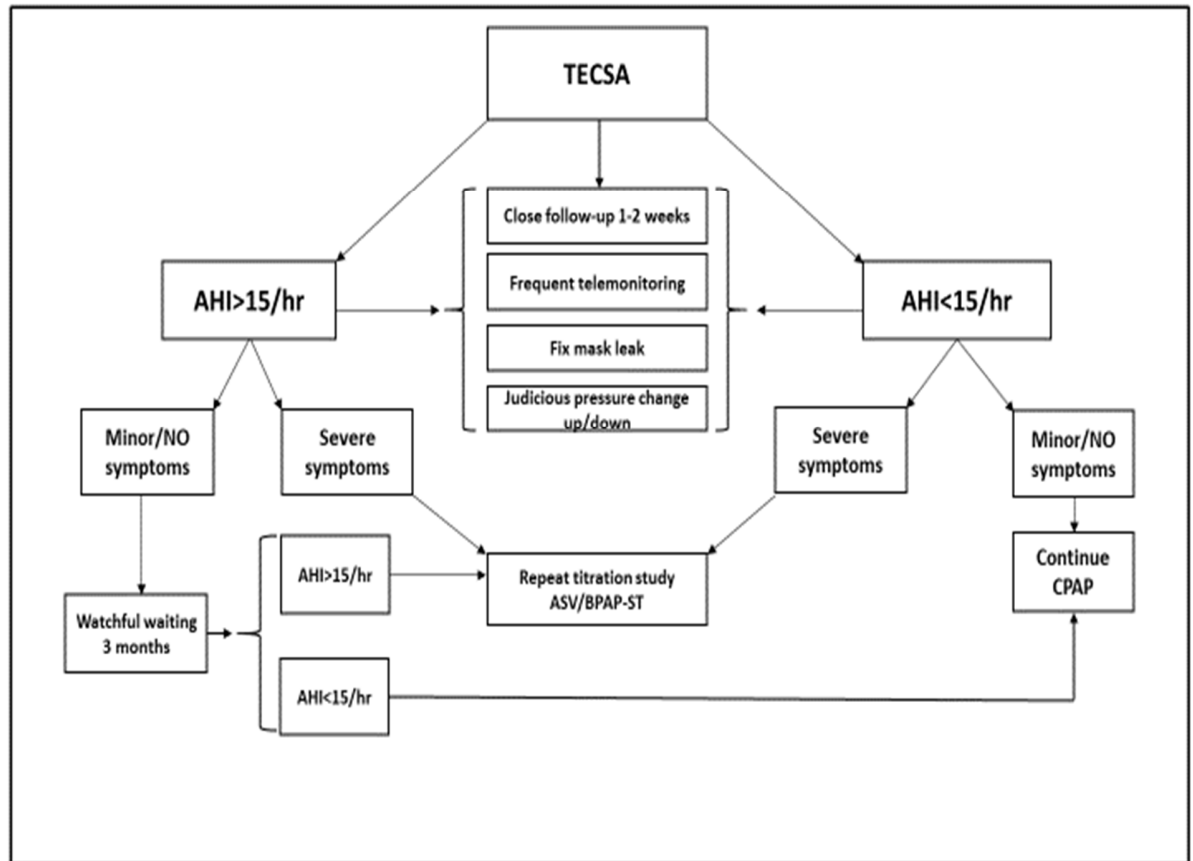
Table 1. TECSA risk factors

1. Demographic factors^{24,53-55}
 - male gender
 - older age
 - lower BMI
2. Medical comorbidities^{56,54,6}
 - Congestive heart failure
 - Coronary artery disease
 - Opioids use
3. Baseline polysomnographic factors^{6,27,53,54,57,23,58}
 - More severe OSA
 - Higher central apnea index
 - Higher mixed apnea index
 - Higher arousal index
4. Titration study factors^{6,23,59}
 - Split-night study
 - Hasty/excessively high titration
 - Mask leak
 - Higher arousal index
 - Lower total sleep time
 - Lower sleep efficiency
 - Higher residual AHI
 - BPAP use

Table 2. Treatment of TECSA - Summary of different modalities

	Mechanism of action	Special considerations	Effectiveness	Cost
PAP therapy				
1. CPAP	*Fixed pressure eliminates obstruction (optimal pressure is a challenge as higher pressures may induce/worsen TECSA and lower pressures leave residual obstructive apneas and hypopneas)	*Close follow-up recommended *High rate of therapy discontinuation in symptomatic patients *Repeat titration required in select patients, may be associated with increased costs	*Spontaneous resolution of TECSA in 53.8-85.7% of patients after 4-28 weeks ²³	300-1000\$
2. BPAP-ST	*EPAP is set to relieve obstruction *IPAP and back-up respiratory rate mitigate hypoventilation	*Avoid high IPAP-EPAP difference (PS) and back-up respiratory rate to prevent hyperventilation *Optimize patient-ventilator synchrony to improve comfort and adherence to therapy	*No direct comparative effectiveness with CPAP * Inferior to ASV ³³ *Effectiveness is dependent on sleep technician proficiency for optimal titration results	2000-4000\$
3. ASV	*EPAP is set to relieve obstruction * PS mirrors ventilation based on breath by breath analysis over 3-4 min window * Dampens the magnitude of hyperventilation	*Limited availability secondary to high cost *Contraindicated in heart failure patients with EF<45% (increased mortality)	*Superior to CPAP/BPAP-ST ^{33,34} * Effectiveness is dependent on sleep technician proficiency for optimal titration results	3000-5000\$
Oxygen	*Decreased carotid body chemosensitivity, and dampens oscillations in ventilatory control	*Hypoxemic patients with cardio-pulmonary comorbidities may benefit from titration studies with O2	*Most effective in patients with CSA-CSB ⁴⁷ *In our experience, O2 is mostly effective when added early on after TECSA appears and persists despite slow and careful upward titration and titrated to keep O2 saturation $\geq 94\%$	200\$/month
Acetazolamide	Widens the CO2 reserve Decreased plant gain	*Limited evidence *Use is extrapolated from other CSA types (primary CSA, CSA secondary to spinal cord injury/disease)	*Evidence is limited	54-89\$ / 30 days

Figure 1. Proposed treatment algorithm



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