Original Article

A systematic review on prevalence and risk factors associated with treatment- emergent central sleep apnea

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Abstract:

INTRODUCTION: Treatment-emergent central sleep apnea (TECSA) is the appearance of central apneas and hypopneas after significant resolution of the obstructive events has been attained using positive airway pressure (PAP) therapy. The aim of the study was to determine the prevalence of TECSA and to understand what factors are associated with its development.

METHODS: PubMed, MEDLINE, Scopus, Web of Science and Cochran Library databases were searched with Mesh headings to locate studies linking TECSA and obstructive sleep apnea (OSA).

RESULTS: Nine studies were identified that reported the prevalence of TECSA ranging from 5.0% to 20.3%. Prevalence of TECSA for studies using only full night titration was between 5.0% and 12.1% where as it was between 6.5% and 20.3% for studies using split-night polysomnogram. The mean effective continuous PAP (CPAP) setting varied between 7.5 cm and 15.2 cm of water for patients in TECSA group and between 7.4 cm and 13.6 cm of water for the group without TECSA.

CONCLUSIONS: The aggregate point prevalence of TECSA is about 8% with the estimated range varying from 5% to 20% in patients with untreated OSA. The prevalence tends to be higher for split-night studies compared to full night titration studies. TECSA can occur at any CPAP setting although extremely high CPAP settings could increase the likelihood. Male gender, higher baseline apnea-hypopnea index, and central apnea index at the time of diagnostic study could be associated with the development of TECSA at a subsequent titration study.

Key words:

Apnea-hypopnea index, central sleep apnea, obstructive sleep apnea, prevalence, treatment-emergent central sleep apnea

Treatment-emergent central sleep apnea (TECSA) or "complex sleep apnea" is characterized by persistence or emergence of central apneas on exposure to positive airway pressure (PAP) device without a backup rate, when the obstructive respiratory events that were noted during the prior diagnostic sleep study or diagnostic portion of split-night sleep study have significantly resolved.[1] The term "complex sleep-disordered breathing" was first described by Gilmartin *et al*.[2] while the term "complex sleep apnea syndrome" was introduced by Morgenthaler *et al*. Currently, the International Classification of Sleep Disorders-3 uses the term TECSA (with complex sleep apnea being the "alternate name") to emphasize the iatrogenic nature of this subtype of CSA syndrome.

CSA can appear on exposure to virtually any treatment modality used to treat obstructive sleep apnea (OSA). Surgical interventions such as tracheostomy,[3] maxillomandibular advancement,[4] and surgery to overcome nasal obstruction[5] could lead to the emergence of central apneas. Even the use of mandibular advancement devices[6,7] has been reported to increase the risk of development of TECSA; all of which suggests that treatments beyond PAP therapy can create this polysomnographic phenomenon. Nevertheless, the most common modality triggering TECSA is continuous PAP (CPAP) or bi-level PAP device without back up rate. The current review focuses on discussing TECSA on exposure to PAP devices without back up rate.[8-16] The primary objective of this review

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is to determine the prevalence of TECSA in OSA patients on 1st time exposure to PAP therapy. The secondary objective is to understand the demographic and polysomnographic risk factors that influence the prevalence of TECSA.

What is the physiological mechanism triggering TECSA on exposure to CPAP? It appears that in patients with heightened chemoreflex sensitivity, CPAP therapy can intermittently decrease the $PaCO_2$ below the apneic threshold. The hypocapnic-induced apneic threshold represents a physiological state-dependent fluctuating numerical value resulting from a small but significant fall in end-tidal $PaCO_2$ (usually 3–4 mmHg) below the eupneic $PaCO_2$.[17] This drop occurs more commonly during the periods of nonrapid eye movement (NREM) sleep when the CO_2 reserve (the gap between eupneic $PaCO_2$ and the apneic threshold) is highly labile.[2] All of this occurs in patients with OSA, who are already predisposed to ventilation instability and central apneas at sleep onset due to decreased and fluctuating oscillatory muscle tone in the upper airways on withdrawal of the "wakefulness drive."[18]

Methods

The preferred reporting items for systematic reviews and meta-analyses statement checklist were used to report the findings of this systematic review [Figure 1].

All the three investigators (Gaurav Nigam, Charu Pathak, Muhammad Riaz) conducted a search independently using the online databases of PubMed, MEDLINE, Scopus, Web of Science and Cochrane Central, Register of Controlled Trials, using selected keywords "treatment-emergent central sleep apnea," "complex sleep apnea," "prevalence," and "risk factors" to locate studies from inception through August 15, 2015. The search also included Mesh terms and phrases in combinations to accommodate for any differences in select terminology in the different databases. Hand searches of the reference lists of relevant articles were completed to identify other pertinent articles. Extensive gray literature and Google Scholar searches were completed to identify the relevant publications that may have been missed by the electronic database search. An example of MEDLINE search strategy: ("Continuous Positive Airway Pressure"[Mesh]) AND "Sleep Apnea, Central"[Mesh], ("Continuous Positive Airway Pressure"[Mesh]) AND "Sleep Apnea, Central"[Mesh] AND "Prevalence"[Mesh], ("Continuous Positive Airway Pressure"[Mesh]) AND "Sleep Apnea, Central"[Mesh] AND "Risk Factors"[Mesh], complex sleep apnea* [tiab], treatment-emergent sleep apnea [tiab], treatment-emergent sleep apnea AND CPAP, and complex CSA* [tiab] AND risk factors* [tiab]. All three investigators independently performed data extraction using a standard data extraction form to determine the eligibility for inclusion. Disagreements among investigators were resolved by consensus opinion.

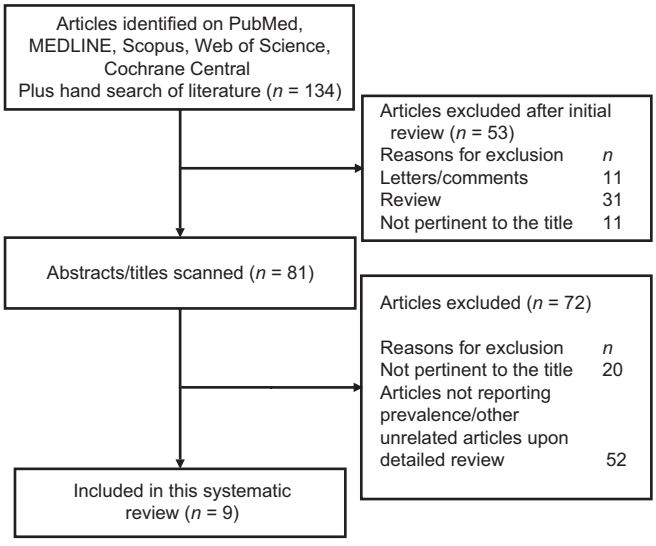

Figure 1: Prevalence of treatment-emergent central sleep apnea using preferred reporting items for systematic reviews and meta-analyses literature search

The quality of each study was individually evaluated according to the guidelines developed by the National Institute for Health and Clinical Excellence. This tool helped to mitigate the heterogeneity in the presented clinical data that may have appeared due to differences among the study designs. An eight point scoring system judged the quality of the study. The following parameters were assessed: (1) Has the case series been collected in more than one center?, (2) Is the hypothesis/aim/objective of the study clearly described?, (3) Are the inclusion and exclusion criteria clearly reported?, (4) Is there a clear definition of the outcomes reported?, (5) Were data collected prospectively?, (6) Is there an explicit statement that patients were recruited consecutively?, (7) Are the main findings of the study clearly described?, and (8) Are outcomes stratified? If a study did not clearly mention one of these key elements, we surmised that it had not been obtained. This approach might have led to some underestimation of the reported characteristics.

Inclusion criteria of this systematic review were (1) Studies including subjects with a new or established diagnosis of OSA, (2) Studies which reported percentage of patients with OSA developing TECSA on exposure to PAP therapy, (3) All studies including patients with one or more cardiovascular co-morbidities such as hypertension, atrial fibrillation, ischemic heart disease, congestive heart failure, and stroke in addition to the presence of sleep-disordered breathing, and (4) Studies that discussed risk factors associated with TECSA. Exclusion criteria were; (1) Studies that did not define what constituted TECSA, (2) Studies that only reported number of patients with TECSA without mention of the total number of OSA patients in the study sample, and (3) Studies that did not conduct in-laboratory CPAP titration study to establish the prevalence of TECSA.

Results

This review identified nine studies that discussed the prevalence of TECSA.[8-16] Five of these studies were conducted in the USA, 2 in Japan, 1 in Germany, and 1 in Australia. Seven of the nine studies were retrospective in design with one study (Cassel *et al*.) being prospective observational and one study being cross-sectional (Dernaika *et al*.). Data in all studies were collected between 2004 and 2009 with fairly good consistency around the definition of TECSA. The sample size of subjects with OSA ranged from 99 (Lehman *et al*.) to 1312 (Endo *et al*.).

Minimum baseline apnea-hypopnea index (AHI) required to proceed with CPAP titration varied between 5 and 20/h. Four studies used full-night CPAP titration (Cassel, Endo, Javaheri, and Yaegeshi *et al*. studies), four studies used titration portion of split-night study (Dernaika, Kuzniar, Morgenthaler, and Pusalavidyasagar *et al*., studies), and one study had subjects from both titration and split-night study (Lehman *et al*.) to estimate prevalence of TECSA. The data on the prevalence of TECSA and assessment of the quality of studies are listed in Table 1.

The prevalence of TECSA varied between studies from 5.0%[10] to 20.3%.[15] Prevalence of TECSA for studies using only full night titration was between 5.0% and 12.1% where as it was between 6.5% and 20.3% for studies using split-night polysomnogram. The average age of patients with TECSA varied between 44 and 65 years while that for patients without TECSA was 47–59 years. Average body mass index (BMI) for patients with TECSA varied between 29 and 36 kg/m^2 while that for patients without TECSA was 26–37 kg/m^2. Male patients made up 81–99% of all subjects with TECSA while they made up 60–86% of all patients without TECSA. The prevalence of TECSA was at 5% (Endo *et al*.) and 6.5% (Javaheri *et al*.) for the two studies that had the largest sample size. In summation, a total of 4375 patients underwent sleep study titration following the diagnosis of OSA, of which 366 patients met the criteria for TECSA. This gives an aggregate point prevalence (percentage of the total number of OSA patients that had TECSA at the time of undergoing titration sleep study) of 8.37%.

Certain factors were associated with increased prevalence of TECSA [Table 2]. Statistically significant associations for increased likelihood of having TECSA included male gender (Lehman, Morgenthaler, and Pusalavidyasagar *et al*. studies) and an older age (Cassel *et al*.). Patients with TECSA in Pusalavidyasagar *et al*. study had a statistically significant lower BMI than patients without TECSA. Certain polysomnographic parameters at baseline polysomnogram are associated with the development of TECSA. Compared to the patients without TECSA, patients with TECSA had a higher baseline AHI (Cassel, Endo, Javaheri, and Lehman *et al*. studies), and higher baseline arousal index (Lehman *et al*.). Higher baseline central apnea index (CAI) (Cassel, Javaheri, Lehman, and Pusalavidyasagar *et al*. studies), and more specifically, an increase in CAI in NREM supine sleep (Yaegashi *et al*.) during baseline study may predict increased likelihood for the appearance of TECSA during a subsequent titration.

Most studies reported the "effective" (i.e., the optimum) CPAP setting leading to TECSA or resolution of OSA with no appearance of TECSA. The mean effective CPAP setting varied between 7.5 and 15.2 cm of water for patients in TECSA group and between 7.4 and 13.6 cm of water for the group of OSA patients without TECSA. In Dernaika *et al*. study the effective absolute CPAP setting (used to treat OSA that inadvertently lead to TECSA) was statistically higher in patients with TECSA than in OSA patients without it. In Javaheri *et al*. study the relationship between CPAP level and CAI was significant only if a select few patients at high CPAP settings were included.

Discussion

The aggregate point prevalence of TECSA in patients undergoing titration study following the diagnosis of sleep-disordered breathing is about 8% although the range of prevalence widely varies between 5% and 20% [Figure 2]. For the studies included in this review, the minimum AHI required at baseline sleep study to proceed with CPAP titration varied between 5 and 20 events/h. Some studies did not mention the baseline AHI threshold that was used to determine eligibility for follow-up titration. In addition to certain demographic and polysomnographic factors, the sample size of patient population and type of sleep study conducted (full night titration vs. split-night), affect the rates of prevalence of TECSA. Two of the three studies that reported the prevalence rate at below 6.5% were studies that had the largest sample size (with a total number of subjects exceeding 1200 in each) with both studies utilizing full night CPAP titration. On the other hand, the two studies with the highest reported prevalence rate for TECSA were studies with small sample size (with a total number of subjects under 200 in each) with both studies utilizing split-night study protocol. There was a trend toward a negative correlation between sample size and prevalence of TECSA [Figure 3]. Split-night studies tended to report a higher prevalence of TECSA than studies that used full night titration results [Figure 2]. One major reason why split-night studies recorded a higher prevalence of TECSA could be that these studies conduct CPAP titration same night only on patients who have a greater severity of OSA (as defined by a higher baseline AHI) observed during the diagnostic portion of the study. Furthermore, limited titration time on split nights may necessitate relatively rapid uptitrations to attain the effective CPAP setting, giving less time for the apneic threshold to adjust, and adapt.

Among polysomnographic factors at baseline sleep study, a higher baseline AHI and CAI were strongly associated with

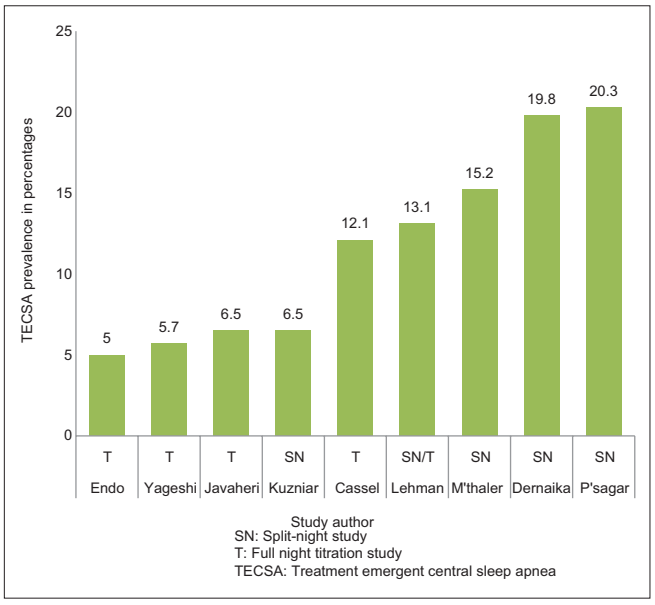

Figure 2: Prevalence of treatment-emergent central sleep apnea in patients with obstructive sleep apnea

Table 1: Summary of major findings from studies on treatment-emergent central sleep apnea

Study Year Location Design	Calendar year for data collection Type of sleep study (SN vs. T)	Definition of TECSA Minimum baseline AHI required to proceed with titration	Total number with TECSA/total number with OSA Best+ CPAP in TECSA/No TECSA	TECSA prevalence@	Average age of TECSA/age of no-TECSA patients in years	Average BMI of TECSA/average BMI of no-TECSA patients in years	Percentage of males in TECSA/ no-TECSA	Study quality★ 1 2 3 4 5 6 7 8
Cassel *et al*. 2011 Germany Prospective observational	Before 10/2009 (over 24 months)	CAI ≥5/h or predominant periodic breathing pattern with otherwise effective CPAP treatment (i.e., <5 obstructive or mixed apneas or hypopneas per hour)	82/675	12.1	59.8±9.7/55.4±11.6	31.8±5.3/32.3±5.8	87/86	✖ ✔ ✔ ✔ ✔
	T	AHI ≥5	7.5±1.6/7.4±1.8					✔ ✔ ✔
Dernaika *et al*. 2007 USA Cross-sectional	9/2004-12/2005	CAI ≥5/h during titration portion of split night in patients who only had OSA during diagnostic portion	23/116	19.8	59.3±12.1/58.6±11.5Ψ	35.9±6.1/36.8±5.9Ψ	NM/NM	✖ ✔ ✔
	SN	AHI ≥20	15.2±2.3/13.6±2.7					✔ ✖ ✖ ✔ ✔
Endo *et al*. 2008 Japan Retrospective	Before 04/2008	Residual CAI was 5 or more per hour or Cheyne-Stokes respiratory pattern became prominent and disruptive after CPAP titration eliminated events defining OSA	66/1312	5.0	43.7±12.1/47.0±12.2Φ	30.1±6.7/28.4±7.8Φ	99/92Φ	✖ ✔ ✔ ✔ ✖
	T	AHI ≥20	NM/NM					✔ ✔ ✔
Javaheri *et al*. 2009 USA Retrospective	06/2006-05/2007 T	CAI ≥5/h on CPAP AHI NM	84/1286 11.0±2/11.6±3	6.5	53±13/53±13¥	33±4/33±6¥	83/85¥	✖ ✔ ✔ ✔ ✖ ✔ ✔ ✔

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Table 1: Contd...

Study Year Location Design	Calendar year for data collection Type of sleep study (SN vs. T)	Definition of TECSA Minimum baseline AHI required to proceed with titration	Total number with TECSA/total number with OSA Best+ CPAP in TECSA/No TECSA	TECSA prevalence@	Average age of TECSA/age of no-TECSA patients in years	Average BMI of TECSA/average BMI of no-TECSA patients in years	Percentage of males in TECSA/ no-TECSA	Study quality* 1 2 3 4 5 6 7 8
Kuzniar *et al.* 2007 USA Retrospective	2003-2005	CAI ≥5/h or Cheyne-stokes respiratory pattern became prominent and disruptive after OSA resolved on CPAP	13/200	6.5	65 (56-71)**/NM	32.1 (30.2-34.6)/ NM	85/NM	✖ ✔ ✖ ✔
	SN	AHI NM	9 (8-11)**/NM					✖ ✖ ✔ ✔
Lehman *et al.* 2007 Australia Retrospective	Before 08/2007	Patients with a CAI of ≥5/h at or near (±1 cm H_2O) prescribed CPAP	13/99	13.1	55.2±16.0/57.4±10.6	33.4±7.9/33.1±5.8	92/79	✖ ✔ ✖
	SN and T	AHI NM	11.0±2.8/9.3±2.5					✔ ✖ ✔ ✔ ✔
Morgenthaler *et al.* 2006 USA Retrospective	01/2004-06/2004	Residual CAI was 5 or more per hour or Cheyne-Stokes respiratory pattern became prominent and disruptive after CPAP titration eliminated events defining OSA	34/223	15.2	52.3±15.2/56.7±13.1	33.0±6.0/34.7±9.8	81/60	✖ ✔ ✔ ✔ ✖
	SN	AHI ≥5	8.4±1.9/8.9±2.5					✔ ✔ ✔
Pusalavidyasagar *et al.* 2006 USA Retrospective	01/2004	CPAP titration eliminated events defining OSAS but if the residual CAI was ≥5 or CSR pattern became predominant and disruptive	34/167	20.3	54.4±16/57.6±12.2	33±5.9/36±10.3	82/64	✖ ✔ ✖ ✔
	SN	AHI ≥5	8.4±1.9/9.1±2.7					✖ ✔ ✔ ✔

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Table 1: Contd...

Study Year Location Design	Calendar year for data collection Type of sleep study (SN vs. T)	Definition of TECSA Minimum baseline AHI required to proceed with titration	Total number with TECSA/total number with OSA Best[+] CPAP in TECSA/No TECSA	TECSA prevalence[@]	Average age of TECSA/age of no-TECSA patients in years	Average BMI of TECSA/average BMI of no-TECSA patients in years	Percentage of males in TECSA/ no-TECSA	Study quality[★] 1 2 3 4 5 6 7 8
Yaegeshi *et al*. 2011 Japan Retrospective	08/2003-07/2008	Residual CAI of 5 or more after CPAP titration eliminated events defining OSA	17/297	5.7	54.8±15.9/58.6±14.7	28.8±6.1/25.7±3.9	88/84	✖ ✔ ✔
	T	AHI ≥20	NM/NM					✔ ✖ ✔ ✔ ✔

✔ = Data are statistically significant (P<0.05); ✖ = Data are not statistically significant. [@]TECSA prevalence per 100 patients with OSA, [¥]Based on data provided for 84 Patients without CSA on the first night of CPAP titration, **Values represent median (IQR), [Ψ]As reported in data from 21 control subjects, [Φ]Data represent mean±SD for all the patients with "pure OSA" (a total of 1196) excluding those with TECSA (a total of 66), central sleep apnea (a total of 14) and mixed breathing pattern (a total of 50), [+]Best CPAP in cm of water pressure (used to treat OSA, inadvertently leading to TECSA or resolution of OSA with no TECSA), ★Quality assessment of the included studies checklist from questions from National Institute for Health and Clinical Excellence 1-8: (1) Case series collected in more than one center?, (2) Is the hypothesis/aim/objective of the study clearly described?, (3) Are the inclusion and exclusion criteria clearly reported?, (4) Is there a clear definition of the outcomes reported?, (5) Were data collected prospectively?, (6) Is there an explicit statement that patients were recruited consecutively? (7) Are the main findings of the study clearly described?, (8) Are outcomes stratified?. TECSA = Treatment-emergent central sleep apnea; No-TECSA = Patients with obstructive sleep apnea but no treatmen-emergent central sleep apnea; SN = Split-night study; T = Full night titration study; NM = Not mentioned; CAI = Central apnea index; CPAP = Continuous positive airway pressure; OSA = Obstructive sleep apnea; IQR = Interquartile range; SD = Standard deviation; AHI = Apnea hypopnea index; BMI = Body mass index; CSR = Cheyne-Stokes respiration; OSAS = Obstructive sleep apnea syndrome

Table 2: Risk factors associated with increased prevalence of treatment-emergent central sleep apnea (by comparing statistically significant data in treatment-emergent central sleep apnea patients to those in obstructive sleep apnea patients without treatment-emergent central sleep apnea, respectively)

Study	High baseline AHI	High baseline CAI	High baseline ArI	High CPAP setting (in cm of water)	Older age	Male gender	Low BMI	Presence of congestive heart failure or ischemic heart disease
Cassel *et al.*	✓	✓	✖	✖	✓	✖	✖	✖ [t]
Dernaika *et al.*	✖	✖	✖	✓	✖	NM	✖	✖
Endo *et al.*	✓	NM	✖	NM	✖	✖	✖	✖
Javaheri *et al.*	✓	✓	✖	✓ [ψ]	✖	✖	✖	✖
Lehman *et al.*	✓	✓	✓	✖	✖	✓	✖	✓
Morgenthaler *et al.*	✖	✖	✖	✖	✖	✓	✖	✖
Pusalavidyasagar *et al.*	✖	✓	NM	✖	✖	✓	✓	✖
Yaegashi *et al.*	✖	✖	NM	NM	✖	✖	✖	✖

✓ = Data are statistically significant (P<0.05); ✖ = Data are not statistically significant. [ψ]In Javaheri *et al.* study relationship between CPAP level and CAI were significant only if a few patients at high CPAP levels were included (r^2=0.43, P=0.008), [t]There was a trend toward more patients with TECSA, compared to no-TECSA being diagnosed with hypertension and coronary artery disease, although values did not reach statistical significance. TECSA = Treatment-emergent central sleep apnea; OSA = Obstructive sleep apnea; AHI = Apnea hypopnea index; CAI = Central apnea index; ArI = Arousal index; CPAP = Continuous positive airway pressure; BMI = Body mass index; NM = Not mentioned

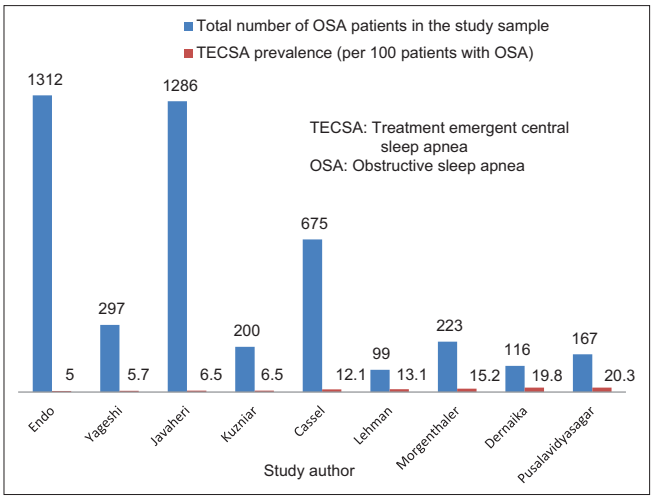

Figure 3: Prevalence of treatment-emergent central sleep apnea in relation to sample size of study population

increased likelihood of TECSA at subsequent titration study as demonstrated in Table 2. TECSA can appear at any tested CPAP setting. Absolute CPAP settings in patients demonstrating TECSA are not much different from those in patients without TECSA unless the required CPAP settings to treat OSA are conspicuously high [Figure 4]. High pressures lead to pressure intolerance and mask leaks, which in turn contribute to sleep fragmentation and central apneas.[19] High pressures could lead to stretching of pulmonary interstitium. At least in mammalian animal model experiments, the activation of juxtacapillary "J" mechanoreceptors in the pulmonary interstitium has been shown to enhance the firing by pulmonary afferent vagal nerve leading to central apneas.[20] These are some of the reasons why extremely high CPAP settings could promote the development of TECSA.

Demographic factors associated with higher prevalence of TECSA as demonstrated in Table 2 include male sex[13-15] older age,[8] and relatively less severe obesity.[15] Congestive heart failure and ischemic heart disease were found to be present in significantly higher number of patients with TECSA in Lehman *et al*. study while Cassel *et al*. found a similar trend that did not reach statistical significance. Of note; older age, male sex, and congestive heart failure are also associated with CSA.[1] This could indicate that TECSA is a form of CSA masked by obstructed airways. Although cardiovascular co-morbidities such as coronary artery disease, congestive heart failure, and hypertension are fairly common in individuals demonstrating TECSA, almost one-third of the patients have no identifiable co-morbidities and still develop TECSA, due to unknown reasons.[21] While there is some available information on demographic and polysomnographic factors that are associated with the appearance of TECSA as described above; clinical or polysomnographic factors that would predict resolution of TECSA while on CPAP therapy have not been well delineated.[22]

TECSA should be viewed as a dynamic polysomnographic phenomenon. The application of PAP promotes restitution of airway patency but at the same time suppresses the normal physiologic rise (2–8 mmHg) in $PaCO_2$ that occurs during

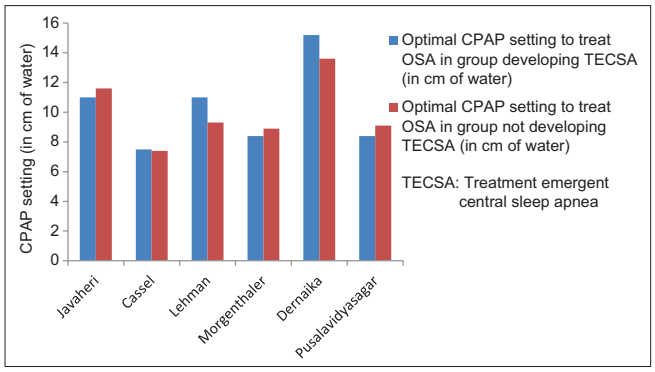

Figure 4: Optimal continuous positive airway pressure setting to treat obstructive sleep apnea in group developing treatment-emergent central sleep apnea versus group not developing treatment-emergent central sleep apnea

stage NREM, and may intermittently bring it below the apneic threshold creating episodes of TECSA.[23] Overtime the apneic threshold which is a fluctuating value readjusts and resets itself making TECSA a transient process. The vast majority of patients will demonstrate the resolution of TECSA with continued CPAP or adaptive servoventilation use within few weeks to few months.[22] While most patients demonstrate gradual resolution of central apneas over weeks to months, 1.5–3% of patients with TECSA may continue to exhibit central apneas on a chronic basis.[7,8,10,11] Furthermore, some patients with sleep-disordered breathing who did not demonstrate TECSA on the first titration study may insidiously start showing TECSA when undergoing re-titration studies few months later.[8] All these polysomnographic scenarios support the dynamic nature of TECSA.

There are several significant implications of these findings. Identifying the prevalence helps us estimate what patient population with untreated OSA might have difficulty with early adherence to CPAP for reasons beyond claustrophobia and pressure intolerance. Identification of risk factors associated with TECSA is equally important. Patients at high risk of TECSA should be candidates for in-laboratory CPAP titration with a rapid transition to PAP device with back up rate if TECSA episodes become frequent, prominent, or disruptive with significant oxygen desaturation.[24] Skipping in-laboratory titration in preference for empirical auto-PAP prescriptions in these patients may lead to worsening of their sleep-disordered breathing and poor PAP adherence.

Our review has certain limitations. The majority of the constituent studies had a retrospective design and had the same limitations as that of any other retrospective study. Although the definition of TECSA was fairly standardized across all studies, the minimum baseline AHI cut-off used to decide when to proceed with CPAP titration varied widely, with some studies not mentioning the AHI cut-off threshold used. This inconsistency could have led to overestimation in prevalence in studies allowing titration only for the most severe categories of OSA. At the same time, this approach made it difficult to estimate the prevalence of TECSA in patients with the mild category of OSA, who might have been selectively excluded prior to titration study. Most studies did not provide data on the amount of time spent in supine sleep during titration with CPAP. It is possible that TECSA, similar to CSA is more frequent in supine sleep position and hence amount of time spent in supine sleep position could affect rates of TECSA prevalence. Some of the studies did not have an adequate sample size, which might have compromised the statistical power of the study. Inconsistencies around the method of conducting sleep study (some using full night titration, some using split-night, and some using a combination of both) might have contributed to the heterogeneity in the estimated prevalence.

Conclusions

The aggregate point prevalence of TECSA in patients who undergo PAP titration study after diagnosis of OSA is about 8% although the range of prevalence varies from 5% to 20%. Prevalence rate may lie at the higher end of the reported range when estimated on the basis of studies conducted on patient populations of limited sample size utilizing split-night study model. Patients with TECSA are more likely to be males. They have higher AHI and CAI compared to patients without TECSA, on their baseline sleep studies. TECSA can occur at any CPAP setting. While 1st time exposure to extremely high CPAP settings in a PAP naïve patient may increase the likelihood of developing TECSA, there is no absolute CPAP setting that clearly precludes or potentiates their development.

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Conflicts of interest
There are no conflicts of interest.

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