The prevalence of treatment-emergent central sleep apnea with mandibular advancement device therapy

TITLE

The prevalence of treatment-emergent central sleep apnea with mandibular advancement device therapy

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ABSTRACT

Study objectives

Treatment-emergent central sleep apnea (TECSA) describes the appearance or persistence of central sleep apnea while undergoing treatment for obstructive sleep apnea (OSA). TECSA is well-studied in continuous positive airway pressure (CPAP) therapy with an estimated prevalence of 8%. Based on few case reports, mandibular advancement devices (MAD) may also provoke TECSA. This study aims to gain insight into the prevalence of TECSA with MAD therapy.

Methods

This retrospective study includes a total of 129 patients with moderate to severe OSA who were treated with a custom-made titratable MAD. Baseline and follow-up sleep studies were compared to identify patients with TECSA. Since different diagnostic criteria to define TECSA are used in literature, prevalence was calculated according to three definitions (TECSA-1, -2, and -3). Demographics, MAD treatment variables, and findings of the diagnostic polysomnography were compared between TECSA and non-TECSA patients to identify possible predictors.

Results

Depending on the definition used, TECSA was found in 3.1% to 7.8% of patients undergoing MAD therapy. TECSA patients had a higher apnea index (AI, 9.2 vs. 2.0 events/h, p=0.042), central apnea-hypopnea index (CAHI, 4.1 vs. 0.2 events/h, p=0.045) and oxygen desaturation

index (ODI, 23.9 vs. 16.3 events/h, p=0.018) at baseline compared to non-TECSA patients. No differences were found in demographics and treatment variables.

Conclusions

These findings demonstrate that TECSA also occurs in patients starting MAD treatment. Patients with TECSA had a higher AI, CAHI, and ODI at baseline compared to non-TECSA patients.

BRIEF SUMMARY

Treatment-emergent central sleep apnea is a well-known phenomenon in patients with obstructive sleep apnea treated with continuous positive airway pressure, however very little is known about its occurrence using a mandibular advancement device. As such mandibular advancement devices are increasingly used, more research on this topic is needed. This study demonstrates that treatment-emergent central sleep apnea also occurs during treatment with a mandibular advancement device, again emphasizing the importance of proper follow-up after the initiation of treatment.

INTRODUCTION

Sleep-related breathing disorders are characterized by disturbed respiratory patterns occurring during sleep. Obstructive sleep apnea (OSA) is marked by repetitive cessation or decrease of airflow due to complete or partial upper airway collapse.[1] In central sleep apnea (CSA), airflow limitation is caused by a lack of ventilatory effort during sleep. There are several manifestations of CSA including idiopathic CSA, high-altitude periodic breathing, Cheyne-Stokes breathing, and drug-induced CSA.[2]

When CSA emerges or persists while undergoing treatment for obstructive sleep apnea (OSA), it is called treatment-emergent central sleep apnea (TECSA), also known as complex sleep apnea. The physiological mechanisms that underpin TECSA in patients with OSA are not yet clarified. Possible mechanisms include ventilatory control instability (high loop gain), low arousal threshold, and prolonged circulation time.[3] In some cases, TECSA appears to be a self-limiting problem that resolves spontaneously with continued treatment. However, in others it persists.[4-6] As treatment compliance is lower in patients with TECSA, early identification could help reduce this risk.[5]

TECSA is well described in continuous positive airway pressure (CPAP) therapy. A systematic review by Nigam and colleagues showed an aggregate point prevalence of TECSA of about 8% across CPAP titration studies,[7] with a range between 5.0%[8] and 20.3%[9]. The exact diagnostic criteria used to define TECSA vary between published studies, contributing to the heterogeneity of results.[10] Besides CPAP therapy, TECSA may also occur in alternative treatment modalities for OSA, such as mandibular advancement devices (MAD), hypoglossal nerve stimulation, and maxillofacial surgery.[11]

MAD therapy, the leading alternative to CPAP for patients with moderate to severe OSA, acts by protruding the mandible and increasing pharyngeal patency.[12] An integrated titratable mechanism in the MAD allows gradual mandibular protrusion in search for maximum therapeutic effect.[13] To date, literature on TECSA in MAD therapy is limited to case reports.[6,14-16] Accordingly, prevalence data are not yet available. This study aimed to determine the prevalence of TECSA in a large cohort of patients treated with MAD. A secondary goal was to identify possible predictors of TECSA in MAD therapy.

METHODS

Study population

For this retrospective study, all patients treated with a custom-made, titratable MAD from January 2019 to June 2021 at the Antwerp University Hospital (Belgium) were screened for inclusion. Patients were eligible if they had moderate to severe OSA (apnea-hypopnea index (AHI) ≥15 events/hour). Patients were excluded in case of absent or incomplete baseline or follow-up sleep studies, if MAD treatment was combined with another treatment modality, or in case of predominant CSA at baseline.

Polysomnography

Diagnosis was based on a type 1 full night polysomnography using standard sleep study equipment, following the American Academy of Sleep Medicine (AASM) guidelines.[17,18] Polysomnography comprises recordings of respiratory data (nasal pressure and thermistor),

thoracoabdominal movements, electrooculography, electroencephalography, electrocardiography, electromyography, pulse oximetry, body position, and snoring.

MAD treatment

In this project, three different custom-made titratable duo-bloc MAD types were used (Narval CC (ResMed, Lyon, France), SomnoMed Flex (SomnoMed, Crows Nest, Australia), and SomnoDent Avant (SomnoMed, Crows Nest, Australia)). Each MAD was fitted at maximal comfortable protrusion (MCP). Thereafter, patients were instructed to titrate the device guided by subjective relief of cardinal symptoms such as snoring and excessive daytime sleepiness, or when reaching the individual physical limits of protrusion. The degree of effective mandibular protrusion was calculated as a percentage of the patient's maximal protrusion (%max) following the titration period.

Follow up

After a titration period, a type 3 monitoring device was used to assess MAD treatment outcome at home (Home Sleep Apnea Test (HSAT)). This examination incorporated nasal pressure and thermistor, thoracoabdominal movements, pulse oximetry, body position, and snoring signals. All sleep recordings were scored manually in a standard fashion by a qualified sleep technician.[1]

Diagnostic criteria of TECSA

Overall treatment success was defined as a reduction in the AHI to ≤10 events/hour and 50% reduction in AHI from baseline. The prevalence of TECSA was calculated according to three definitions, to facilitate comparison with existing literature (Table 1). For the first and most

broad definition, referred to as TECSA-1, patients had to show predominant central sleep apnea at follow-up, defined as more than five central events per hour and >50% of apneas central. The second and most frequently used definition (TECSA-2) included all patients with predominant CSA at follow-up (cf. TECSA-1), who in addition had effective treatment of OSA (i.e., decrease of >50% in obstructive apnea-hypopnea index). Finally, the third and most strict definition (TECSA-3) included patients meeting TECSA-2 criteria in whom the central apnea-hypopnea index (CAHI) was less than five at baseline (i.e., only new emergent CSA). For all definitions, CSA could not be better explained by another identifiable comorbidity such as CSA with Cheyne-Stokes breathing (CSB) or CSA by a drug or substance (ICSD-3, AASM 2014).[10]

Statistical analysis

Statistical analysis and data management were performed using IBM SPSS Statistics (version 28.0. Armonk, NY) and JMP Pro software (version 16.0, SAS institute Inc., Cary, NC, USA). Descriptive statistics are presented as medians and 1st and 3rd quartiles [Q1-Q3] unless otherwise specified. For comparisons between groups, Fisher's exact test and Mann-Whitney U test were used for categorical and continuous variables, respectively. The Wilcoxon test was used for intragroup comparisons. A p-value of less than 0.05 was considered statistically significant.

Ethical approval

Ethical approval for this study was obtained from institutional review boards of the Antwerp University Hospital (Belgian registration number: B30020110946).

RESULTS

Demographics

A total of 225 patients started treatment with a MAD and were screened for inclusion. 129 patients met the eligibility criteria and were included for further analysis (Figure 1). The median time interval between MAD treatment initiation and follow-up HSAT (i.e., titration period) was 98 [93.5-119] days. Baseline characteristics are summarized in Table 2.

Overall treatment response

At baseline, 93 patients (72.1%) were diagnosed with moderate OSA (15≤AHI<30 events/hour) and 36 patients (27.9%) with severe OSA (AHI ≥30 events/hour). Overall, MAD therapy reduced the median AHI from 24.6 [18.6-32.0] events/hour to 6.9 [3.1-12.4] events/hour ($p<0.001$). 85 patients (65.9%) met the criteria for treatment success. The obstructive apnea-hypopnea index (OAHI) as well as the 3% oxygen desaturation index (ODI) both decreased significantly (22.0 [17.6-31.0] to 6.1 [2.9-10.6] events/hour, $p<0.001$, and 16.6 [10.0-23.5] to 6.4 [3.2-11.3] events/hour, $p<0.001$, respectively). However, the CAHI didn't change under MAD treatment (0.3 [0.0-1.4] to 0.3 [0.0-1.3] events/hour, $p=0.701$).

Prevalence

The prevalence of TECSA according to the different definitions is shown in Table 1. A total of 10 patients met the diagnostic criteria of TECSA-1, corresponding to a prevalence of 7.8% (95% CI 3.1-12.4%). TECSA-2 and TECSA-3 were seen in 4.7% (95% CI 1.0-8.3 %) and 3.1% (95% CI 0.1-6.1%) of the study population, respectively.

Characteristics of TECSA patients

As TECSA-2 is the most frequently used definition, this subgroup will be discussed more in detail. Baseline demographics such as age, gender, and BMI did not differ between patients with and without TECSA-2 (Table 3).

The polysomnographic results from the diagnostic night showed a trend to a higher baseline AHI in patients with TECSA-2 compared to patients without TECSA-2 (33.8 [24.4-44.8] vs. 24.4 [18.4-30.9] events/h, p=0.089). The CAHI was significantly higher at baseline in the TECSA-2 subgroup (4.1 [0.2-9.2] vs 0.2 [0.0-1.3] events/h, p=0.045; Figure 2). Furthermore, both the apnea index (AI, 9.2 [4.7-15.4] vs. 2.0 [0.3-6.5] events/h, p=0.042), as well as the ODI (23.9 [19.8-49.4] vs. 16.3 [9.8-23.4] events/h, p=0.018), were significantly higher in TECSA patients. The total sleep time with saturation below 90% was comparable between both groups (1.3 [0.7-1.9] vs. 0.9 [0.1-4.6] % of TST, p=0.823). There were no significant between-group differences in sleep architecture, with a comparable total sleep time, sleep efficiency, and time spent in REM and non-REM sleep stages. Furthermore, the titrated MAD protrusion was comparable in both groups (79.5 [76.8-82.7] vs. 81.8 [74.4-90.5] %max, p=0.516).

DISCUSSION

To the best of our knowledge, this is the first study that determined the prevalence of TECSA in patients treated with MAD. According to the definition selected, a prevalence between 3.1% and 7.8% was found in the present test population. Bearing in mind that TECSA with MAD therapy is only reported a few times in literature, this relatively high prevalence is somewhat surprising and may indicate an underdiagnosis of the problem. However, the clinical relevance of TECSA remains questionable. It is interesting to note that of the six TECSA-

2 cases in this study, five were able to continue MAD treatment. Therefore, it can be stated that the consequences of TECSA in patients under MAD therapy, at least in terms of treatment adherence and symptom control, were rather limited and that diagnosis of TECSA does not always have clinical consequences.

Although many theories have been postulated, the pathophysiological mechanism of TECSA has not yet been clarified. CPAP and MAD therapy cannot simply be compared, but there might be a substantial overlap. Presumably, TECSA is caused by an anatomical and physiological vulnerability to upper airway collapse in combination with ventilatory control instability.[19,20] A likely mechanism involves the relief of upper airway obstruction: if upper airway patency is restored by treatment, the efficiency of CO_2 excretion is increased and hypocapnia can be induced. When the $PaCO_2$ value falls below the apnea threshold, a central apnea will occur.[21,22] Over the course of weeks to months of treatment, ventilatory control adapts, resulting in the resolution of central apneas. This is supported by Salloum and colleagues, who showed that chemosensitivity and apnea threshold decreased significantly with the use of CPAP.[23]

Stanchina and colleagues showed that loop gain was higher in TECSA patients in whom central apneas persisted after one month of treatment.[24] With high loop gain as a possible contributor to persistent TECSA, loop gain-lowering interventions (e.g., acetazolamide and oxygen) might be useful for adjunct therapy in these patients. Acetazolamide, a carbonic anhydrase inhibitor, increases ventilation mainly by producing metabolic acidosis. This results in a reduction of loop gain without affecting other physiological traits.[25] In our population, one patient with persistent TECSA was treated with acetazolamide and showed a complete resolution of all central apneas.

In addition to CPAP and MAD treatment, the emergence of central events has also been described with other treatment modalities. Patel et al[26] found TECSA in 3.3% of the patients who underwent upper airway stimulation. Generally, these central events tended to be temporary and self-limiting. However, in some individuals, particularly those experiencing persistent central events, an inadequate or excessive stimulation amplitude may contribute to the development of TECSA. Modifying the stimulation parameters has been shown to effectively eliminate central events in these cases.[27]

The occurrence of TECSA after maxillomandibular advancement (MMA) surgery was reported by Goodday and Fay[28] at 1.8%. Meanwhile, Ho et al[29] found TECSA in 1% of their cases when the same diagnostic criteria were applied. TECSA has also been documented in patients with OSA who underwent therapeutic tracheotomy[30,31] and after surgical relief of nasal obstruction.[32]

The prevalence of TECSA with MAD treatment in our population is circa 5%, which is slightly lower than the reported prevalence of 8% with CPAP therapy.[7] A possible explanation for this difference might be the longer time interval between the start of treatment and the follow-up sleep study in MAD therapy.[11] Whereas MAD treatment outcome in our study was assessed after a titration period of several months, patients with PAP-related TECSA are diagnosed immediately upon initiation of treatment, i.e., during the CPAP titration study. Javaheri and colleagues performed a retrospective study of 1288 patients who underwent treatment with CPAP. 6.5% of patients showed CSA during CPAP titration. Interestingly, only 1.5% of these patients continued to have CSA with long-term use of CPAP.[4] A similar downward trend in prevalence over time has been demonstrated in a prospective study of

675 patients by Cassel and colleagues. During the initial CPAP titration study, the prevalence of TECSA was 12.2%. However, this prevalence rate was reduced to 6.9% at follow-up polysomnography with CPAP three months later.[33] Since TECSA seems to resolve spontaneously in most patients with ongoing treatment, the longer interval may partly explain this lower prevalence. However, further research is needed to better understand this phenomenon in patients treated with MAD.

The definition of TECSA is diverse in literature. However, the prevalence may be underestimated or overestimated depending on the diagnostic criteria. To address this issue, we calculated the prevalence of TECSA in our population using multiple definitions to get a more comprehensive understanding.

Despite the different diagnostic criteria applied among prior studies, they all share the presence of CSA while undergoing treatment for primary OSA. In our study, we labeled these patients as TECSA-1. However, this definition does not require effective treatment of obstructive events. As this might be a key element of the pathophysiological mechanism of TECSA, this is a prerequisite for diagnosis in most studies. Therefore, patients with CSA at follow up and effective treatment of obstructive events were designated TECSA-2. An important limitation of these first two definitions is that patients may already have a significant number of central events at baseline. Even though patients must have predominant OSA (usually defined as most events being obstructive), there is no fixed upper limit on the number of central events at baseline. Thus, since there might be concurrent CSA at baseline, some studies make a distinction with new-emergent CSA (i.e., <5 central events per hour at baseline).[4,34] This corresponds with the TECSA-3 definition. However, due to the strict diagnostic criteria, this definition has the risk of underestimating the problem.

This study has some limitations, mainly due to the retrospective study design. Treatment follow-up was assessed by HSAT in all patients and was compared to a baseline in-lab polysomnography. Since the HSAT does not measure sleep, the recording time is used instead of total sleep time, leading to a possible overestimation of the effectiveness of MAD treatment on one hand, and to an underestimation of the prevalence of TECSA on the other hand.[35] Another limitation is related to the prevalence of TECSA: as TECSA occurs only in a limited number of patients, associations between baseline characteristics and the presence of TECSA are based on only a few patients. However, since the primary focus of this study was to determine the prevalence of TECSA in MAD therapy, this was an additional exploratory part of the study. Finally, this study did not include long-term follow-up of patients. Further research should be undertaken to investigate the natural course of TECSA in MAD treatment.

Overall, this study offers insight into the prevalence of TECSA with MAD therapy. Our results showed that TECSA occurred in approximately 5% of patients starting treatment with a MAD. Given the increasing number of patients treated with oral appliances, this finding highlights the importance of adequate follow-up after treatment initiation.

Although patients with TECSA had more severe sleep apnea, the onset of TECSA remains largely unpredictable. Therefore, further research should focus on determining pathophysiological traits (e.g., loop gain, arousal threshold, …) that could predict TECSA. Recognizing patients who are at higher risk for TECSA may be helpful to identify those who are more likely to benefit from alternative therapies.

ABBREVIATIONS

AASM	American Academy of Sleep Medicine
AHI	Apnea-hypopnea index
AI	Apnea index
BMI	Body-mass index
CAI	Central apnea index
CAHI	Central apnea-hypopnea index
CO_2	Carbon dioxide
CPAP	Continuous positive airway pressure
CSA	Central sleep apnea
CSB	Cheyne-Stokes breathing
HSAT	Home sleep apnea testing
MAD	Mandibular advancement device
MCP	Maximal comfortable protrusion
OAHI	Obstructive apnea-hypopnea index
OAI	Obstructive apnea index
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnea
$PaCO_2$	Partial pressure of carbon dioxide in the arterial blood
REM	Rapid eye movement
TECSA	Treatment-emergent central sleep apnea

FIGURES

Fig. 1. Flow diagram of patient inclusion

[1]Hypoglossal nerve stimulator, acetazolamide

Fig. 2. Baseline and follow-up AHI and CAHI of patients without and with TECSA-2. ♦: Median CAHI. Abbreviations: TECSA: Treatment-Emergent Central Sleep Apnea; AHI: Apnea-Hypopnea Index; CAHI: Central Apnea-Hypopnea Index.

TABLES

Table 1
Prevalence of treatment-emergent central sleep apnea

	CAHI ≥5/h	CAI >50% of AI	≥50% reduction in OAHI	CAHI baseline <5/h	Prevalence		95% confidence interval	
							Lower	Upper
TECSA-1	✓	✓	-	-	10/129	7.8%	3.1%	12.4%
TECSA-2	✓	✓	✓	-	6/129	4.7%	1.0%	8.3%
TECSA-3	✓	✓	✓	✓	4/129	3.1%	0.1%	6.1%

Abbreviations: TECSA: Treatment-Emergent Central Sleep Apnea; CAHI: Central Apnea-Hypopnea Index; CAI: Central Apnea Index; OAHI: Obstructive Apnea-Hypopnea Index

Table 2
Clinical characteristics

	All patients
	n = 129
Demographics	
Gender, No. male (%)	108 (83.7)
Age (years)	50.9 (44.4-58.4)
BMI (kg/m^2)	27.1 (25.5-30.2)
ESS	9.0 (6.0-12.0)
Benzodiazepine, No. (%)	4 (3.1)
Opioids, No. (%)	1 (0.8)
Polysomnography	
TST (min)	412 (370-444)
SEI (%)	82.2 (75.9-89.1)
REM (%/TST)	19.5 (15.6-23.9)
N3 (%/TST)	17.3 (11.9-24.0)
AHI (/h)	24.6 (18.6-32.0)
AI (/h)	2.2 (0.3-6.8)
OAI (/h)	1.1 (0.1-4.1)
OAHI (/h)	22.0 (17.6-31.0)
CAI (/h)	0.2 (0.0-1.3)
CAHI (/h)	0.3 (0.0-1.4)
ODI (/h)	16.6 (10.1-23.6)
Sat ≤ 90% (% of TST)	1.0 (0.1-3.5)
Mandibular advancement device	
Type	
Narval CC, No. (%)	20 (15.5)
Somnomed Flex, No. (%)	72 (55.8)
SomnoMed Avant, No. (%)	27 (28.7)
Protrusion	
Protrusion (%max)	81.5 (74.1-89.4)

Data presented as median (Q1-Q3). Abbreviations: BMI: Body Mass Index; ESS: Epworth Sleepiness Scale; TST: Total Sleep Time; SE: Sleep Efficiency Index; REM: Rapid Eye Movement; AHI: Apnea-Hypopnea Index; AI: Apnea Index; OAI: Obstructive Apnea Index; OAHI: Obstructive Apnea-Hypopnea Index; CAI: Central Apnea Index; CAHI: Central Apnea-Hypopnea Index; ODI: Oxygen Desaturation Index; Sat: Saturation.

Table 3

Clinical variables of patients with and without TECSA-2 at follow-up

	No TECSA-2	TECSA-2	
	n = 123	n = 6	P-value
Demographics			
Gender, No. male (%)	103 (83.7)	5 (83.3)	0.999
Age (years)	50.9 (43.9-58.3)	54.5 (43.4-64.5)	0.527
BMI (kg/m^2)	27.2 (25.4-30.5)	26.8 (25.8-27.8)	0.467
ESS	9.5 (6.0-12.0)	8.0 (4.8-11.8)	0.539
Baseline polysomnography			
TST (min)	413 (374-444)	348 (294-450)	0.164
SEI (%)	82.3 (76.5-89.2)	72.1 (58.2-89.0)	0.180
REM (%/TST)	19.5 (15.6-23.7)	20.5 (15.3-28.7)	0.611
N3 (%/TST)	17.3 (11.9-24.1)	19.0 (14.2-26.1)	0.675
AHI (/h)	24.4 (18.4-30.9)	33.8 (24.4-44.8)	0.089
AI (/h)	2.0 (0.3-6.5)	9.2 (4.7-15.4)	***0.042***
OAI (/h)	1.0 (0.1-4.0)	2.5 (0.8-7.7)	0.343
OAHI (/h)	22.0 (17.5-29.0)	30.1 (19.9-40.2)	0.309
CAI (/h)	0.2 (0.0-1.2)	4.1 (0.2-9.2)	***0.043***
CAHI (/h)	0.2 (0.0-1.3)	4.1 (0.2-9.2)	***0.045***
ODI (/h)	16.3 (9.8-23.4)	23.9 (19.8-49.4)	***0.018***
Sat ≤ 90% (%/TST)	0.9 (0.1-4.6)	1.3 (0.7-1.9)	0.823
Mandibular advancement device			
Protrusion (%max)	81.8 (74.1-90.5)	79.5 (76.8-82.7)	0.516

Data presented as median (Q1-Q3). Abbreviations: TECSA: Treatment-Emergent Central Sleep Apnea; BMI: Body Mass Index; ESS: Epworth Sleepiness Scale; TST: Total Sleep Time; SE: Sleep Efficiency Index; REM: Rapid Eye Movement; N3: Non-Rapid Eye Movement Sleep Stage 3; AHI: Apnea-Hypopnea Index; AI: Apnea Index; OAI: Obstructive Apnea Index; OAHI: Obstructive Apnea-Hypopnea Index; CAI: Central Apnea Index; CAHI: Central Apnea-Hypopnea Index, ODI: Oxygen Desaturation Index; Sat: Saturation.

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