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Treatment-emergent central sleep apnea in patients treated with a mandibular advancement device

Hédi Aïssani [a,*], Jean-Daniel Kün-Darbois [a,b,c], Clémence Moreau [d], Frédéric Gagnadoux [b,c], Wojciech Trzepizur [b,c], on behalf of the IRSR Pays de la Loire Sleep Cohort Study Group

[a] CHU Angers, Department of Maxillo-facial surgery, F-49933, Angers, France
[b] CHU Angers, Department of Respiratory and Sleep Medicine, F-49933, Angers, France
[c] Univ Angers, Faculty of Medicine, F-49000 Angers, France
[d] CHU Angers, Delegation for Clinical Research and Innovation, F-49933, Angers, France

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ABSTRACT

Objectives: Treatment-emergent central sleep apnea (TECSA) is well established in continuous positive airway pressure therapy but was barely studied in mandibular advancement device (MAD) treatment. This study aims to evaluate the prevalence of TECSA in patients treated with a MAD and to determine its risk factors and clinical relevance.

Materials and methods: A total of 139 patients from the IRSR Pays de la Loire Sleep Cohort suffering from snores or obstructive sleep apnea syndrome (OSAS) and treated with a custom-made titratable MAD were included. Baseline and follow-up sleep recordings enabled identification of TECSA patients. Comparative analyses were carried out between TECSA and non-TECSA groups to identify potential risk factors. Clinical relevance of TECSA in both groups was assessed through baseline and follow-up Pichot's self-assessment questionnaire for depressive symptoms (QD2A), 36-item short form survey (SF-36) and Epworth Sleepiness Scale (ESS) scores.

Results: According to the definition selected, a prevalence between 0 % and 5.04 % was found for TECSA in the present study. No statistical differences were found in terms of treatment characteristics, sleep architecture, demographic data or comorbid conditions, although there was a trend towards a higher prevalence of arterial hypertension in TECSA-1 than in non-TECSA group (42.9 % vs 25.4 % respectively, $p = 0.379$). Baseline ESS showed a trend towards a higher score in TECSA-1 patients compared to non-TECSA patients (13/24 vs 10/24 respectively, $p = 0.074$), with a high proportion of TECSA-1 patients suffering from excessive daytime sleepiness before initiation of treatment (85.7 %, vs 52.4 % in non-TECSA patients, $p = 0.124$). No statistical differences were found regarding delta Pichot's QD2A and ESS scores between baseline and follow-up although there was a trend towards higher ESS scores at follow-up in TECSA-1 group compared to non-TECSA patients. Median delta SF-36 score for the General health scale was significantly lower in TECSA-1 and there was a trend towards lower scores for Mental health category in TECSA-1 patients.

Conclusions: TECSA is a rare phenomenon that can occur in patients treated with a MAD for an OSAS. Clinical, polysomnographic and treatment-related risk factors have yet to be reassessed in larger cohorts. These findings suggest probably poorer subjective clinical outcomes in terms of sleepiness and quality of life in patients with MAD-related TECSA.

Abbreviations: OSAS, obstructive sleep apnea syndrome; PSG, polysomnography; CPAP, continuous positive airway pressure; MAD, mandibular advancement devices; AHI, apnea-hypopnea index; ICSD-3, International Classification of Sleep Disorders-Third Edition; TECSA, treatment-emergent central sleep apnea; AI, apnea index; OAI, obstructive apnea index; OAHI, obstructive apnea-hypopnea index; CAI, central apnea index; CAHI, central apnea-hypopnea index; 3 % ODI, 3 % oxygen desaturation index; TST, total sleep time; Tsat 90 %, percentage of nighttime spent with oxygen saturation <90 %; REM, rapid-eye movement; ESS, Epworth Sleepiness Scale; EDS, excessive daytime sleepiness; SF-36, 36-item Short Form Survey; CSA, central sleep apnea; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

* Corresponding author. Service de Chirurgie Maxillo-Faciale, CHU d'Angers, Cedex, 49933, ANGERS, France.
E-mail address: Hedi.Aissani@chu-angers.fr (H. Aïssani).

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1. Introduction

Mandibular advancement devices (MAD) have emerged as the principal alternative to continuous positive airway pressure (CPAP) for the treatment of obstructive sleep apnea syndrome (OSAS). According to French clinical guidelines, MAD therapy is recommended as an appropriate first-line treatment option for snoring and mild to moderate OSAS in patients without severe cardiovascular comorbidity or as a second line option in patients intolerant to CPAP. Despite a lower impact of MAD on decreasing the apnea-hypopnea index (AHI), both treatments have been shown to have a similar impact on clinical outcomes, including sleepiness, and cardiovascular outcomes [1–5].

According to the International Classification of Sleep Disorders-Third Edition (ICSD-3), Treatment-Emergent Central Sleep Apnea (TECSA) is characterized by persistence or emergence of central sleep apneas on exposure to CPAP devices while obstructive events have resolved [6]. TECSA is a well-known phenomenon in patients treated with CPAP, with a prevalence ranging from 5.0 % to 20.3 % [7]. TECSA's natural course remains mostly unknown and its potential clinical impact is still controversial [8]. TECSA appears to resolve spontaneously with time in most cases. It may also persist leading to a higher risk of therapy discontinuation [9]. TECSA may also occur with alternative OSAS treatments, such as maxillo-mandibular advancement, upper airway surgery or tracheostomy [10]. The prevalence of TECSA in patients treated with a MAD has been assessed to date in only one study and ranged between 3.1 % and 7.8 % depending on TECSA definition [11].

The main objective of the study was to assess the prevalence of TECSA in a large prospective cohort of snoring and OSAS patients treated with a MAD. The secondary objectives were to identify risk factors for the occurrence of TECSA and to assess the impact of TECSA on treatment symptomatic efficacy and adherence.

2. Materials and methods

2.1. Study population and design

The study was performed on the *Institut de Recherche en Santé Respiratoire [IRSR] des Pays de la Loire cohort study group*. Consecutive patients treated in Angers University Hospital for OSAS or snores with a MAD, between January 2011 and October 2017 with available pre-treatment and follow-up sleep-recordings data were included in the study. All participants gave an informed consent for their participation in the study. This prospective study was approved by the University of Angers ethics committee (Comité d'Ethique du Centre Hospitalier Universitaire d'Angers, No.2007/17; Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé, No 07.207bis).

2.2. MAD treatment

Four different types of titratable bi-bloc MAD with proven efficacy in treating OSAS and snores were used in the present study. Two of them were custom-made MAD: AMO® device and SomnoDent® device (SomnoMed, Ancenis, France) [12,13]. The third one was a customizable, thermoplastic MAD: BluePro® device (BlueSom, Paris, France) [14]. The last one was a custom-made computer-aided design/computer-aided manufacturing (CAD/CAM) bi-bloc MAD: Narval CC® (ResMed, Lyon, France) [15].

All patients were fitted with the chosen device by a qualified oral and maxillo-facial surgeon or a dentist. Patients underwent MAD titration following a standardized protocol: once fitted with the MAD at 70 % of maximal jaw active propulsion, patients underwent an acclimatization period during which the mandible was incrementally advanced by 1-mm steps every 1 or 2 weeks until symptom relief or the maximum comfortable limit of advancement was achieved [14]. The degree of mandibular propulsion was expressed in millimeters and in percentage of the patient's maximal jaw active propulsion. Adherence to treatment was assessed through two criteria: the reported number of nights per week and number of hours per night MAD was used.

2.3. Sleep recordings

At baseline, patients underwent polysomnography or type-III overnight respiratory recordings (CID 102 LX, Cidelec, Sainte-Gemmes sur Loire, France). All patients underwent type-III overnight respiratory recordings after MAD titration. Respiratory events were scored manually using recommended criteria [16]. Respiratory events were classified as obstructive or central, giving respectively the obstructive apnea index (OAI) and obstructive apnea-hypopnea index (OAHI) and the central apnea index (CAI) and central apnea-hypopnea index (CAHI). Of note, a systematic characterization of hypopneas (obstructive versus central) was conducted at the Angers Hospital as part of this prospective cohort. 3 % Oxygen desaturation index (3 % ODI) was defined as the average number of desaturations $\geq$3 % lasting at least 10 s per hour. Snoring index was defined as the number of snoring events per hour. Percentage of nighttime spent with oxygen saturation <90 % (Tsat 90 %) was extracted from sleep recordings.

For patients who underwent overnight polysomnography, specific data were extracted: total sleep time (TST), time spent in rapid-eye movement (REM) and N3 sleep stages.

2.4. Subjective clinical outcomes

Subjective daytime sleepiness was assessed by the Epworth Sleepiness Scale (ESS). An ESS score >10/24 defined an excessive daytime sleepiness (EDS) [17]. Depression symptoms were assessed using the Pichot's QD2A score and depressive syndrome was retained for a score $\geq$7/13 [18,19]. 36-Item short form survey (SF-36) was used to measure patient's quality of life [2,20].

2.5. TECSA definitions

To facilitate comparison with existing literature the prevalence of TECSA was calculated according to 3 definitions [11]. TECSA-1 was defined as a follow-up CAHI$\geq$5/h with predominant central sleep apnea (CSA) (central apneas >50 % of apnea index); TECSA-2 included, amongst patients meeting the TECSA-1 criteria, those who presented a decrease of >50 % in OAHI (treatment effectiveness); TECSA-3 included patients meeting TECSA-2 criteria with only new emergent CSA, i.e. those with a baseline CAHI<5/h. According to the ICSD-3 definition of TECSA, CSA must not be attributable to another diagnosis such as drug-induced CSA or Cheyne-Stoke Breathing associated with congestive heart failure [6].

2.6. Statistical analysis

All statistical analysis were performed using the R software (version 4.0.5). Descriptive statistics were presented as numbers and percentages for qualitative variables, and as medians with 1st and 3rd quartiles for quantitative variables. For comparisons between groups, Fisher's exact test and Mann-Whitney test were used for qualitative and quantitative variables, respectively. In order to visualize differences between non-TECSA and TECSA-1 patients, adapted graphical solutions were used to represent the evolution of ESS scores over time, as well as the distribution of the differences in ESS between inclusion and the follow-up visit. A p-value<0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics of the study population

A total of 139 patients were included in the analysis. The study

population consisted of predominantly male (74.1 %) and overweight patients (BMI 26.1 [24.5; 28.7] kg/m^2). The prevalence of cardiovascular, metabolic and respiratory comorbidities was low (26.3 % and 0.78 % for arterial hypertension and cardiac arrhythmia respectively, 3.76 % for diabetes and 5.34 % for chronic obstructive pulmonary disease) (Table 1). None of the included patients was diagnosed with chronic heart failure. A retrospective analysis of patient's electronic medical records found no opioid use among TESCA patients at the time of the sleep recordings.

A total of 93 patients underwent polysomnography (66.90 %) and 46 patients underwent type-III overnight respiratory recording (33.09 %) at baseline. Median AHI in the study population was 30.0 [17.0; 35.0] events/hour at baseline, among which 52.5 % of patients presented with severe, 28.8 % with moderate and 15.1 % with mild OSAS (Table 2). Median ESS score in the study population was 10 [6.0; 13.0]/24, with 54.1 % of patients suffering from EDS (Table 3). The most frequently used MAD models in the population study were the customizable thermoplastic BluePro® (47.5 %) and the titratable custom-made AMO® device (43.9 %). SomnoDent® device and Narval CC® were rarely used (7.91 % and 0.72 % respectively). Median effective MAD propulsion in the study population was of 7.0 [5.0; 8.0] millimeters and 70 [58; 80] % of the maximal jaw active propulsion (Table 4).

3.2. Comparisons between non-TECSA and TECSA patients

A total of 7 patients met the diagnostic criteria of TECSA-1, leading to a prevalence of 5.04 % (95 % CI 2.0–10.1 %). Only 2 patients met the diagnostic criteria of TECSA-2, resulting in a prevalence of 1.44 % (95 % CI 0.2–5.1 %). No patient met the diagnostic criteria of TECSA-3 in the study population. In consequence, analyses were carried out on the TECSA-1 group, which is the largest in our population and refers to the broadest definition of TECSA.

There were no statistical differences between non-TECSA and TECSA-1 groups in terms of general characteristics or comorbidities. However, the prevalence of arterial hypertension in TECSA-1 group was almost twice as high as in non-TECSA group (42.9 % vs 25.4 % respectively, $p = 0.379$) (Table 1).

We did not find any statistical differences between both groups regarding baseline sleepiness (ESS), quality of life (SF-36) and depressive symptoms (QD2A). However, a trend to higher baseline ESS scores was observed in TECSA-1 patients compared to non-TECSA patients (13/24 vs 10/24 respectively, $p = 0.074$), with a high proportion of TECSA-1 patients suffering from EDS (85.7 %, vs 52.4 % in non-TECSA patients, $p = 0.124$) (Table 3).

No significant differences were found between non-TECSA and TECSA-1 groups in terms of OSAS severity, except for CAHI which was as expected significantly higher in TECSA-1 group (2.96 [1.49; 5.86] events/hour, vs 0.46 [0.12; 1.31] events/hour in non-TECSA group, $p =$

Table 1
Baseline demographics and comorbidities of the study population.

Variables	Missing data	All n = 139	Non-TECSA n = 132	TECSA-1 n = 7	*p*
General characteristics					
Age (years)	–	51.5 [44.8; 59.3]	51.7 [44.7; 59.5]	51.3 [50.0; 55.7]	0.904
Male sex	–	103 (74.1 %)	98 (74.2 %)	5 (71.4 %)	1.000
BMI (kg/m^2)	–	26.1 [24.5; 28.7]	26.1 [24.4; 28.5]	27.5 [26.3; 30.9]	0.118
Comorbidities					
Arterial hypertension	6	35 (26.3 %)	32 (25.4 %)	3 (42.9 %)	0.379
Cardiac arrhythmia	10	1 (0.78 %)	1 (0.82 %)	0 (0.00 %)	1.000
Diabetes	6	5 (3.76 %)	5 (3.97 %)	0 (0.00 %)	1.000
COPD	8	7 (5.34 %)	7 (5.65 %)	0 (0.00 %)	1.000
Current smoking	3	32 (23.5 %)	32 (24.8 %)	0 (0.00 %)	0.199

Data are expressed as median [IQR] for quantitative variables and as numbers and percentages for qualitative variables. The *p*-value corresponds to that obtained using comparison tests (Exact Fisher for qualitative variables, and Mann-Whitney for quantitative variables) between non-TECSA and TECSA-1 patients. TECSA: treatment-emergent central sleep apnea; BMI: body mass index; COPD: chronic obstructive pulmonary disease.

Table 2
Baseline sleep recordings data of the study population.

Variables	Missing data	All n = 139	Non-TECSA n = 132	TECSA-1 n = 7	*p*
OSAS severity					
Snores (events/hour)	–	205 [83.5; 341]	206 [84.8; 353]	186 [33.0; 240]	0.219
AI (events/hour)	–	3.21 [0.94; 9.16]	3.21 [0.94; 8.89]	2.40 [1.61; 13.4]	0.593
AHI (events/hour)	–	30.0 [17.0; 35.0]	30.0 [16.8; 35.0]	30.0 [26.5; 32.0]	0.636
OSAS subtypes	–				0.820
AHI <5		5 (3.60 %)	5 (3.79 %)	0 (0.00 %)	
5 ≤ AHI <15		21 (15.1 %)	20 (15.2 %)	1 (14.3 %)	
15 ≤ AHI <30		40 (28.8 %)	39 (29.5 %)	1 (14.3 %)	
AHI ≥30		73 (52.5 %)	68 (51.5 %)	5 (71.4 %)	
OAI (events/hour)	–	2.24 [0.47; 7.91]	2.22 [0.50; 7.91]	2.28 [0.42; 7.88]	0.958
OAHI (events/hour)	–	27.0 [14.9; 32.9]	27.0 [15.0; 33.2]	26.2 [17.6; 28.5]	0.600
CAI (events/hour)	–	0.28 [0.00; 0.96]	0.27 [0.00; 0.94]	0.77 [0.37; 3.36]	0.065
CAHI (events/hour)	–	0.50 [0.12; 1.46]	0.46 [0.12; 1.31]	2.96 [1.49; 5.86]	0.006
3 % ODI (events/hour)	–	17.0 [10.0; 29.0]	16.0 [10.0; 29.2]	21.0 [16.5; 28.0]	0.418
Tsat 90 % (%/TST)	–	0.00 [0.00; 3.50]	0.00 [0.00; 3.00]	2.00 [0.50; 4.50]	0.229
Specific polysomnography data					
TST (minutes)	46	443 [401; 483]	442 [401; 483]	471 [448; 486]	0.421
REM (%/TST)	46	21.8 [16.8; 24.9]	21.7 [16.7; 24.9]	23.3 [22.5; 24.8]	0.447
N3 (%/TST)	46	20.5 [16.3; 25.2]	20.6 [16.3; 25.2]	19.6 [16.5; 22.9]	0.769

Data are expressed as median [IQR] for quantitative variables, and as numbers and percentages for qualitative variables. The p-value corresponds to that obtained using comparison tests (Exact Fisher for qualitative variables, and Mann-Whitney for quantitative variables) between non-TECSA and TECSA-1 patients. TECSA: treatment-emergent central sleep apnea; A(H)I: apnea (-hypopnea) index; OA(H)I: obstructive apnea (-hypopnea) index; CA(H)I: central apnea (-hypopnea) index; 3 % ODI: 3 % oxygen desaturation index; Tsat 90 %: percentage of nighttime spent with oxygen saturation <90 %; TST: total sleep time; REM: rapid eye movement sleep; N3: N3 sleep stage.

Table 3
Subjective clinical outcomes' scores for the study population at baseline.

Variables	Missing data	All n = 139	Non-TECSA n = 132	TECSA-1 n = 7	*p*
ESS (/24)	6	10.0 [6.00; 13.0]	10.0 [6.00; 13.0]	13.0 [10.0; 17.5]	0.074
EDS (ESS≥ 10/24)	6	72 (54.1 %)	66 (52.4 %)	6 (85.7 %)	0.124
SF-36					
Physical functioning	24	95.0 [90.0; 95.0]	95.0 [90.0; 95.0]	90.0 [90.0; 97.5]	0.836
Role physical	8	100 [75.0; 100]	100 [75.0; 100]	75.0 [37.5; 100]	0.186
Role emotional	6	100 [66.7; 100]	100 [66.7; 100]	66.7 [66.7; 100]	0.311
Vitality	6	45.0 [35.0; 55.0]	45.0 [35.0; 55.0]	45.0 [30.0; 55.0]	0.727
Mental health	9	68.0 [56.0; 76.0]	68.0 [56.0; 76.0]	72.0 [56.0; 78.0]	0.926
Social functioning	5	75.0 [62.5; 100]	75.0 [62.5; 100]	75.0 [62.5; 81.2]	0.661
Bodily pain	5	70.0 [57.5; 80.0]	70.0 [57.5; 80.0]	80.0 [62.5; 80.0]	0.793
General health	6	65.0 [55.0; 80.0]	65.0 [51.2; 78.8]	65.0 [57.5; 80.0]	0.915
QD2A (Pichot's score)	11	1.50 [0.00; 4.00]	1.00 [0.00; 4.00]	2.00 [1.50; 5.50]	0.367

Data are expressed as median [IQR] for quantitative variables, and as numbers and percentages for qualitative variables. The p-value corresponds to that obtained using comparison tests (Exact Fisher for qualitative variables, and Mann-Whitney for quantitative variables) between non-TECSA and TECSA-1 patients. TECSA: treatment-emergent central sleep apnea; ESS: Epworth Sleepiness Scale; EDS: excessive daytime sleepiness; SF-36: 36-Item Short Form Survey; QD2A: self-assessment questionnaire for depressive symptoms.

0.006). Sleep architecture was comparable between both groups for patients who underwent a baseline polysomnography (Table 2).

Good adherence to MAD therapy was achieved in the study population with a median use of 7.0 [6.0; 7.0] nights per week and 7.0 [6.0; 7.0] hours per night with no significant differences between both groups. No statistical differences were found in terms of frequency of use between different MAD models in both groups, neither regarding the treatment characteristics (Table 4). The median time interval between MAD treatment initiation and follow-up overnight respiratory recording was 10 [6,17] months with a trend towards a longer follow-up time in TESCA patients.

3.3. Clinical outcomes evolution under MAD therapy

Changes in OSAS severity variables under treatment in non-TECSA and TECSA-1 patients are shown in Table 5.

The evolution of the three different subjective clinical outcomes (SF-36, QD2A and ESS) between baseline and follow-up in non-TECSA and TECSA-1 patients is shown in Table 6 and Figs. 1 and 2. Median delta ESS score was equal in both groups (−2 [−6; 1] and −2 [−6; 1], p = 0.899), however median ESS score at T1 in TECSA-1 group was twice as high as in non-TECSA group (12 [8,14]/24 in TECSA-1 group vs 6 [3, 9]/24 in non-TECSA group, p = 0.899). Fig. 1 shows a similar downward trend of ESS in both groups under MAD treatment. However, baseline ESS appears to be higher in TECSA-1 group and remains so at follow-up.

Table 4
Treatment characteristics of the study population.

Variables	Missing data	All n = 139	Non-TECSA n = 132	TECSA-1 n = 7	*p*
Treatment characteristics					
MAD model	–				0.708
AMO®		61 (43.9 %)	58 (43.9 %)	3 (42.9 %)	
SomnoDent®		11 (7.91 %)	10 (7.58 %)	1 (14.3 %)	
Narval®		1 (0.72 %)	1 (0.76 %)	0 (0.00 %)	
BluePro®		66 (47.5 %)	63 (47.7 %)	3 (42.9 %)	
Nights per week	28	7.00 [6.00; 7.00]	7.00 [6.00; 7.00]	7.00 [5.50; 7.00]	0.589
Hours per night	29	7.00 [6.00; 7.00]	7.00 [6.00; 7.00]	6.00 [5.00; 6.00]	0.071
Effective propulsion (millimeters)	11	7.00 [5.00; 8.00]	7.00 [5.00; 8.00]	7.00 [5.50; 9.00]	0.800
Effective propulsion (/MJAP)	34	0.70 [0.58; 0.80]	0.70 [0.58; 0.80]	0.62 [0.56; 0.71]	0.224

Data are expressed as median [IQR] for quantitative variables, and as numbers and percentages for qualitative variables. The p-value corresponds to that obtained using comparison tests (Exact Fisher for qualitative variables, and Mann-Whitney for quantitative variables) between non-TECSA and TECSA-1 patients. TECSA: treatment-emergent central sleep apnea; MAD: mandibular advancement device; MJAP: maximal active jaw propulsion.

Table 5
Changes in OSAS severity variables between T0 and T1 for non-TECSA and TECSA-1 patients.

Variables	Non-TECSA (n = 132)		TECSA-1 (n = 7)	
	T0	T1	T0	T1
Snores (events/hour)	206 [84.8; 353]	36.0 [9.50; 158]	186 [33.0; 240]	20.0 [17.5; 33.0]
AI (events/hour)	3.21 [0.94; 8.89]	0.76 [0.13; 1.93]	2.40 [1.61; 13.4]	3.33 [3.04; 4.74]
AHI (events/hour)	30.0 [16.8; 35.0]	7.00 [3.00; 16.0]	30.0 [26.5; 32.0]	13.0 [10.0; 21.0]
OAI (events/hour)	2.22 [0.50; 7.91]	0.28 [0.00; 1.30]	2.28 [0.42; 7.88]	0.54 [0.34; 1.08]
OAHI (events/hour)	27.0 [15.0; 33.2]	6.25 [2.91; 15.0]	26.2 [17.6; 28.5]	4.98 [2.65; 13.4]
CAI (events/hour)	0.27 [0.00; 0.94]	0.13 [0.00; 0.59]	0.77 [0.37; 3.36]	2.73 [2.55; 3.84]
CAHI (events/hour)	0.46 [0.12; 1.31]	0.27 [0.00; 0.95]	2.96 [1.49; 5.86]	8.02 [7.20; 10.9]
3 % ODI (events/hour)	16.0 [10.0; 29.2]	10.0 [5.00; 17.5]	21.0 [16.5; 28.0]	18.0 [14.0; 24.0]

Data are expressed as median [IQR].
OSAS: obstructive sleep apnea syndrome; TECSA: treatment emergent central sleep apnea; A(H)I: apnea (-hypopnea) index; OA(H)I: obstructive apnea (-hypopnea) index; CA(H)I: central apnea (-hypopnea) index; 3 % ODI: 3 % oxygen desaturation index.

The difference between median delta QD2A score in both groups was not statistically significant (−1 [−2; 0] vs 0 [−2; 2] respectively for non-TECSA and TECSA-1 patients, p = 0.429). Median delta SF-36 score for the General health scale was significantly lower in TECSA-1 group (−8 [−25; −1] in TECSA-1 group vs 5 [−5; 15] in non-TECSA-group, p = 0.028). No statistical differences were found in median delta SF-36 for the other seven scales, but a trend towards lower scores for Mental health category was observed in TECSA-1 patients (−2 [−10; 3] in TECSA-1 group vs 4 [−4; 12] in non-TECSA group, p = 0.052).

Table 6
Comparison between T0 and T1 (Epworth Sleepiness Scale, QD2A, SF-36) for non-TECSA and TECSA-1 patients.

Variables	Non-TECSA (n = 132)			TECSA-1 (n = 7)			*p*
	T0	T1	Δ T1-T0	T0	T1	Δ T1-T0	
ESS	10 [6; 13]	6 [3; 9]	−2 [-6; 1]	13 [10; 18]	12 [8; 14]	−2 [-6; 1]	0.899
QD2A	1 [0; 4]	0 [0; 2]	−1 [-2; 0]	2 [2; 6]	3 [2; 6]	0 [-2; 2]	0.429
SF-36							
PF	95 [90; 95]	95 [90; 100]	0 [-5; 5]	90 [90; 98]	90 [90; 90]	−3 [-8; 5]	0.492
RP	100 [75; 100]	100 [75; 100]	0 [0; 0]	75 [38; 100]	63 [50; 75]	−13 [-25; 19]	0.470
RE	100 [67; 100]	67 [67; 100]	0 [0; 0]	100 [67; 100]	50 [33; 92]	−17 [-33; 0]	0.179
VT	45 [35; 55]	55 [45; 65]	5 [0; 19]	45 [30; 55]	38 [31; 40]	0 [-5; 9]	0.183
MH	68 [56; 76]	76 [60; 84]	4 [-4; 12]	72 [56; 78]	62 [50; 74]	−2 [-10; 3]	0.052
SF	75 [63; 100]	88 [63; 100]	0 [-13; 25]	75 [63; 81]	63 [53; 81]	−6 [-13; 0]	0.442
BP	70 [58; 80]	80 [68; 80]	0 [0; 13]	80 [63; 80]	68 [58; 77]	−6 [-13; 0]	0.061
GH	65 [51; 79]	70 [60; 84]	5 [-5; 15]	65 [58; 80]	55 [48; 63]	−8 [-25; −1]	0.028

Data are expressed median [IQR], and p-values compare the delta between T0 and T1 of non-TECSA versus TECSA-1 patients using a Mann-Whitney test.
TECSA: treatment-emergent central sleep apnea; ESS: Epworth sleepiness scale; QD2A: self-assessment questionnaire for depressive symptoms; SF-36: 36-Item Short Form Survey; PF: physical functioning; RP: role physical; RE: role emotional; VT: vitality; MH: mental health; SF: social functioning; BP: bodily pain; GH: general health.

4. Discussion

To our knowledge, this is the largest study to assess the prevalence of TECSA in patients treated with a MAD, and the first to do so on a prospective cohort. We found a prevalence of 5.04 %, 1.44 % and 0 % for TECSA-1, -2 and -3 respectively. This study is also the first to assess the clinical impact of TECSA in patients treated with a MAD. Median delta SF-36 score for the General health scale was significantly lower in TECSA-1 patients and there was a trend towards lower scores for Mental health category in TECSA-1 group. Baseline and follow-up ESS showed a trend towards a higher score in TECSA-1 patients compared to non-TECSA patients, with a high proportion of TECSA-1 patients suffering from EDS before treatment initiation.

According to the 2014 ICSD-3, TECSA is characterized by the persistence or emergence of CSA (which cannot be explained by another disorder) on exposure to CPAP devices without a backup rate while initial obstructive respiratory events have resolved [6]. This new definition clarifies what was previously described as "complex sleep-disordered breathing", or "complex sleep apnea syndrome" and emphasizes the iatrogenic nature of the phenomenon [21,22]. TECSA has been widely studied in OSAS patients treated with CPAP devices. An overall incidence of 6.5 % for CPAP-related TECSA has been reported in the largest study so far [23]. An aggregate point prevalence of 8 % with an estimated range varying from 5.0 % to 20.3 % has been found in a systematic literature review [7]. Although CPAP therapy is specifically mentioned in the ICSD-3 definition of TECSA, a growing number of studies have highlighted the fact that TECSA may also occur with alternative treatment modalities of OSAS such as tracheostomy, hypoglossal nerve stimulation or maxillomandibular advancement surgery [24–26]. To date, the occurrence of TECSA after MAD therapy has been rarely studied [11,27–31].

According to the definition selected, a prevalence between 0 % and 5.04 % was found in the present study. Despite MAD being the main alternative to CPAP in OSAS treatment, only two retrospective studies assessed the incidence of TECSA in MAD population and the potential risk factors.

Ciavarella et al. assessed the occurrence of TECSA in a cohort of 56 patients treated with a MAD for OSAS. In their study, any patient showing the emergence or persistence of CSA during the follow-up PSG was considered TECSA, without defined CSA threshold. Following this overly broad definition of TECSA, they found that 16 out of 56 patients belonged to what could be called the "TECSA-group", giving a prevalence of 40 % for TECSA in this article. This definition was not used in the present work because we consider it is too broad and it is not clinically relevant [31].

Hellemans et al. carried out a retrospective study to assess the prevalence of TECSA in a cohort of 129 patients treated with a MAD. The prevalence of TECSA was assessed after a median time interval of 3 months following MAD initiation. The authors proposed three definitions of TECSA that we decided to replicate in our study to standardize results. They found higher TECSA prevalences than in our study (7.8 %, 4.7 % and 3.1 % for TECSA-1, 2 and 3 respectively) [11].

A possible explanation for the low prevalence of MAD-related TECSA compared to the reported prevalence of CPAP-related TECSA could be the delay between the initiation of treatment and the diagnosis of TECSA. While TECSA recorded by CPAP softwares are immediately identified during diagnostic sleep studies, MAD-related TECSA are

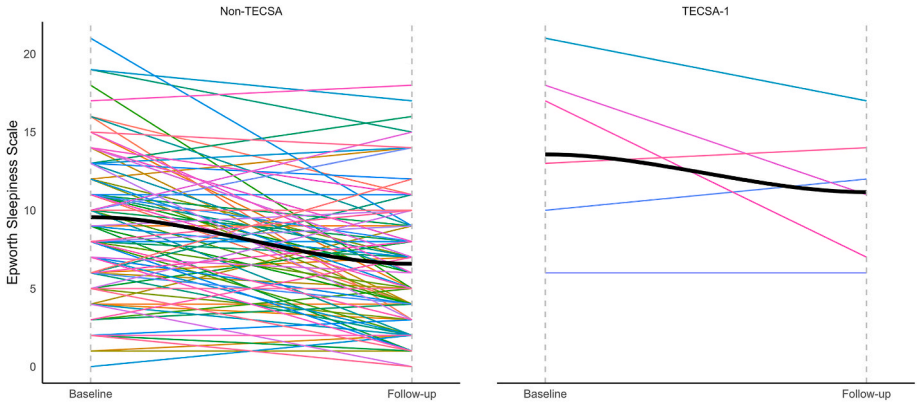

Fig. 1. Individual ESS scores trajectories during follow-up in non-TECSA and TECSA-1 patients.

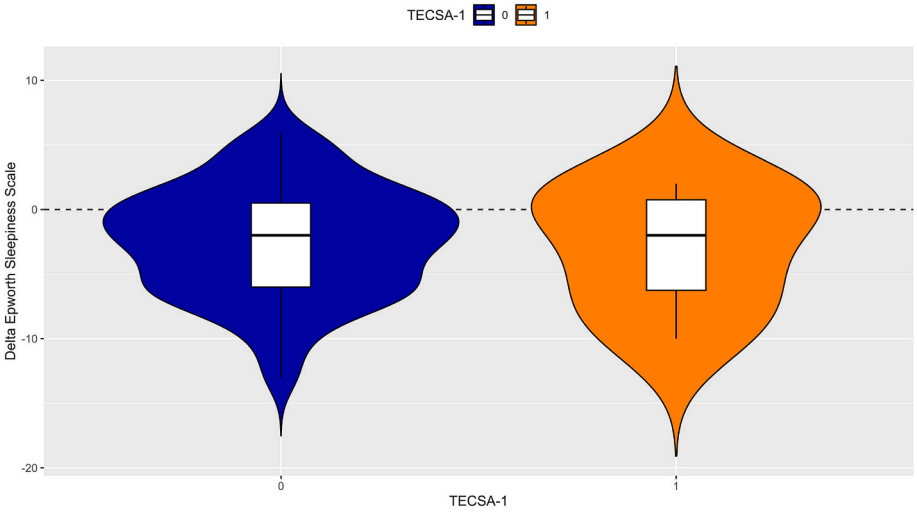

Fig. 2. Violin plots comparing Delta Epworth Sleepiness Scale distribution in non-TECSA and TECSA-1 patients.

discovered during a second recording, usually made several months after the initial polysomnography, as in our study. Furthermore, several studies have shown that TECSA tends to resolve spontaneously in a significant number of cases [23,32]. Liu et al. proposed different trajectories for the natural course of TECSA in a very large CPAP database study including 133 006 patients assessed by PSG at week 1 and week 13. The overall prevalence of TECSA was 3.5 % in their study. Among these patients, TECSA was transient in 55.1 %, persistent in 25.2 %, or emergent in 19.7 % [9]. The natural course of TECSA with non-CPAP therapies has not been as well studied yet, mainly because TECSA is not systematically re-assessed in most studies, but cases of spontaneous resolution exist in the literature [30,33]. In our study population, the median time interval between MAD treatment initiation and follow-up sleep recording was 10 months. Therefore, we can assume that the relatively lower prevalence of TECSA observed in our study and more generally in most studies assessing the prevalence of this phenomenon with non-CPAP treatments of OSAS is at least partly due to the spontaneous resolution of some of the cases ("transient-TECSA") with ongoing treatment.

Another reason that could explain the differences observed in literature in terms of TECSA's prevalence may be the lack of comparability between CPAP and MAD populations regarding demographic data, comorbid conditions and polysomnographic parameters. In our study population, MAD treated patients seemed younger, less severely obese, had fewer metabolic and cardiovascular comorbidities and relatively less severe OSAS than patients treated with CPAP in the same cohort [34]. As some of these parameters are described in the literature as potential predictive factors of CPAP-related TECSA, such as high baseline AHI or cardiovascular comorbidities, we can assume that their lower prevalence in patients treated with a MAD partly explains the lower incidence of TECSA in this population [8].

Lastly, the diversity of diagnostic criteria used to define TECSA, as well as the multiplicity of methodologies employed in the literature may contribute to the variability of the results obtained in terms of prevalence [7].

To address this issue and facilitate comparisons between studies, we chose to use the diagnostic criteria defined in the largest MAD related-TECSA study to date [11]. TECSA-1 is the broadest definition of TECSA, shared by most studies. However, this definition does not take into account the resolution of obstructive events and may lead to an overestimation of the phenomenon. TECSA-2 refines the definition of TECSA-1 by taking into consideration the effectiveness of OSAS treatment, defined by a $\geq$50 % reduction in OAHI under MAD therapy. TECSA-3 can be compared to "emergent-TECSA" or "truly emergent-CSA", adding to the two previous definitions a baseline CAHI<5/h [9,23]. Nevertheless, this definition is probably too restrictive to properly define TECSA and may lead to an underestimation of the phenomenon. In our study, none of the patients fulfilled the diagnostic criteria for TECSA-3.

Many potential risk factors associated with CPAP-related TECSA have been highlighted in the literature, including demographic data (older age, male sex, lower BMI), comorbid conditions (coronary artery disease, hypertension, chronic heart failure, atrial fibrillation, stroke), polysomnographic characteristics (higher baseline AHI, CAI and arousal index, increased CAI in non-REM-sleep) and titration factors (for example excessive titration or air leak, higher residual AHI under CPAP-therapy) [8]. However, little is known about the potential risk factors associated with MAD-related TECSA. Ciavarella et al. did not show any statistical differences between non-TECSA and TECSA patients in their study regarding demographic data, comorbid conditions, polysomnographic parameters or MAD characteristics [31]. Hellemans et al. found that TECSA-2 patients had significantly higher baseline CAHI, AI and 3 % ODI than non-TECSA patients. Still, no statistically significant differences were found regarding demographic data or MAD characteristics. Furthermore, potential association between TECSA and comorbid conditions were not assessed in their study [11]. Our results are in line with these studies. We did not identify any statistically significant risk factors for MAD-related TECSA in our study. No significant differences were found in terms of demographic data and comorbid conditions, although there seemed to be a trend towards a higher prevalence of arterial hypertension in TECSA-1 than in non-TECSA group. Similarly, baseline ESS showed a trend that did not reach statistical significance to a higher score in TECSA-1 patients compared to non-TECSA patients with a high proportion of TECSA-1 patients suffering from EDS before initiation of treatment. No other potential risk factors were found in the study population, especially in terms of MAD characteristics or sleep architecture. Of note, 52.5 % of patients had severe OSAS at baseline. In accordance with French clinical guidelines, MAD were prescribed for patients with mild to moderate OSAS or who were intolerant to CPAP in this cohort. The relatively high percentage of patients with severe OSAS in our study is therefore linked to a high number of patients intolerant to CPAP and is also consistent with other studies performed on the *Institut de Recherche en Santé Respiratoire [IRSR] des Pays de la Loire cohort study group* [14]. Although a higher baseline AHI is suspected to be a risk factor for TECSA, the high rate of severe OSAS in our study probably did not constitute a selection bias as no statistically significant difference was found between non-TECSA and TECSA-1 patients regarding AHI.

The clinical relevance of TECSA remains controversial [8,10,23].

Even if TECSA appears to resolve spontaneously in most cases, it may also persist and in this case, it seems to be associated with a higher risk of poor adherence and therapy discontinuation [9,23,35]. However, little is known about the impact of TECSA on compliance to MAD therapy. Hellemans et al. noted that of the six TECSA-2 cases in their study population, five were able to continue MAD treatment and only one had residual fatigue and was subsequently successfully treated with CPAP [11]. These results are consistent with ours, with a good adherence to MAD therapy and no statistical differences found in terms of compliance to treatment between TECSA-1 and non-TECSA groups in our study population. We did not find either any statistical differences in our study population regarding delta Pichot's QD2A and delta ESS scores between baseline and follow-up. However, there appeared to be a trend towards higher ESS scores at follow-up in TECSA-1 group compared to non-TECSA patients under treatment. Thus, MAD therapeutic efficacy appeared to be similar between non-TECSA and TECSA-1 patients in the study population, but as TECSA-1 patients were sleepier at baseline, they remained so at T1. Median delta SF-36 score for the General health scale was significantly lower in TECSA-1 group and there was a trend towards lower scores for Mental health category in TECSA-1 patients. Overall, subjective clinical outcomes appeared to be poorer at follow-up in patients with TECSA under MAD treatment. Thus, symptomatic impact of TECSA remains a central question and may determine the eventual clinical management of this pathology.

Clinical management of TECSA remains controversial. Considering TECSA is a self-limited and transient phenomenon in most cases, some authors suggest a wait-and-see strategy without changing treatment modalities, and an objective reassessment of therapeutic efficacy after several months to allow ventilatory control to self-regulate [8,10,30]. However, it may be difficult not to intervene if patients remain symptomatic or present with severely impaired PSG characteristics under treatment. Such patients should probably be reassessed earlier with a new sleep recording. Increasing or decreasing MAD advancement might be relevant, as inadequate setting of the device could contribute to the pathophysiology of MAD-related TECSA [28,36]. Several other treatment modalities, such as CPAP, adaptative servo-ventilation or acetazolamide might be effective adjuncts, as they showed efficacy or promising results in CPAP-related TECSA, yet no studies have been carried out to recommend their use in MAD-related TECSA [8,10,35,37].

The present study has some limitations. First, it is limited by the relatively small sample size, despite being the largest studied MAD-TECSA population to date. Its prospective design enabled reliable collection of demographic and clinical characteristics of the patients. Moreover, we did not have echocardiographic data for these patients. This is an observational study, and current recommendations on central apneas only suggest echocardiography in the presence of clinical signs suggestive of heart failure. None of the patients exhibited any such signs or symptoms. Due to the low prevalence of TECSA, our statistical comparisons were based on a small number of patients, which made it difficult to identify any potential risk factors of this phenomenon. Furthermore, the very small number of TESCA patients did not allow for investigation of the prognostic impact of this diagnosis, particularly from a cardiovascular perspective. Yet, this is the first study suggesting probably poorer subjective clinical outcomes in terms of sleepiness and quality of life in patients with MAD-related TECSA.

5. Conclusions

Although it is a rare and mostly transient phenomenon, clinicians should be aware of MAD-related TECSA as it may be associated with poorer clinical results. Systematic follow-up sleep studies and clinical assessments would enable early detection of symptomatic patients whose TECSA does not resolve spontaneously over the time. In such cases, clinicians should consider modifying MAD advancement or use of alternative therapies on an individual basis.

To our knowledge, this study is the first to assess the clinical impact of TECSA in patients treated with a MAD. Further research will be required to assess the potential predictive factors associated with MAD-related TECSA in larger cohorts, to clarify the underlying pathophysiological mechanisms and to determine its possible long-term consequences regarding adherence to treatment and clinical outcomes.

CRediT authorship contribution statement

Hédi Aïssani: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jean-Daniel Kün-Darbois:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Clémence Moreau:** Writing – review & editing, Validation, Software, Data curation. **Frédéric Gagnadoux:** Writing – review & editing, Supervision. **Wojciech Trzepizur:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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