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Treatment Emergent Central Sleep Apnea Evaluation in Patients Treated with Mandibular Advancement Device

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Abstract: The aim of the present cohort study was to evaluate the possible occurrence of central sleep apnea (CSA) in patients with obstructive sleep apnea (OSA) after treatment with a mandibular advancement device (MAD). In this case, 56 patients with OSA treated with MAD were enrolled. Inclusion criteria were age over 20 years, body mass index (BMI) less than 34 kg/m^2, diagnosis of OSA confirmed by polysomnography (PSG), and MAD therapy for OSA. Exclusion criteria were smoking, medications for neurological disorders or a history of cervical head injury, and comorbidities (arrhythmias, congenital heart disease, stroke, heart failure or lung disease). Apnea-Hypopnea Index (AHI), Oxygen Desaturation Index (ODI), Obstructive Sleep Apnea (OSA), Central Sleep Apnea (CSA) and Mixed Apnea were extracted from the PSGs before (T0) and after three months of treatment (T1). Paired-sample *t*-tests and the Wilcoxon Signature Rank test were performed to evaluate differences in PSG indices at T1 and T0. OSA, CSA, AHI, ODI showed a noticeable reduction after MAD therapy, but a limited number of patients showed a dramatic increase in TCSA. The presence of TECSA in the course of MAD treatment is a condition that should be taken into consideration when needing to treat an OSA patient.

Keywords: OSA (obstructive sleep apnea); TECSA (treatment emergent central sleep apnea); MAD (mandibular advancement device)

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1. Introduction

Obstructive sleep apnea syndrome (OSAS) is a common sleep disorder caused by the repetitive collapse of the upper airway during sleep interrupting (apnea) or reducing (hypopnea) the flow of air. The Apnea-Hypopnea Index (AHI) is calculated using the mean number of apnea and hypopnea events per hour and defines the severity of OSAS as follows: absence of sleep apnea < 5 events, mild sleep apnea from 5 to 15 events, moderate sleep apnea from 15 to 30 events and severe more than 30 events [1]. OSA syndrome is a really common disease, it is the second respiratory disorder in order of frequency, preceded by asthma. In terms of epidemiology, it has an incidence ranging at 2–5%. This appears to be more common in males and older people [2]. Although it is a very common condition there is inadequate public health knowledge on the subject and this is one reason why it is estimated that between 80% and 90% of people with OSA are undiagnosed [3]. There are several risk factors that contribute to the development of obstructive apneas. The anatomy of some structures can contribute to create a narrower oropharyngeal space, reducing the lumen of the upper airway (UAW): craniofacial alterations, increased tongue base, amygdala and uvula, maxillomandibular deficiencies. Obesity is another important risk factor as it leads to an increase in neck circumference and a predisposition in the reduction of air space. Supine sleep position predisposes to obstructive apnea because it results in gravitational retro-position of the tongue [1]. Diagnosis is usually made by polysomnography (PSG), a test that allows assessment of both neurological activity and cardio-respiratory parameters during sleep [4].

OSAS has a negative impact on the health and behavior and the scientific literature has described many morbidities associated with OSAS such as cardiovascular and cerebrovascular pathologies: hypertension, increased risk of congestive heart failure, myocardial infarction, cardiac arrhythmias and stroke, also cognitive disorders such as deficiencies in memory and attention, behavioral disorders and also metabolic disorders [5–8]. An Increase of masticatory muscles activity during sleep is showed in many researches [9]. This condition also called sleep bruxim is evaluated in patients with OSA and characterized by rhythmic (phasic) or nonrhythmic (tonic) movement [10]. Therefore, it is important to diagnose and treat this disease to avoid the development of worse health consequences. Continuous positive airway pressure (CPAP) introduced by Sullivan in 1981 [11] is still considered the gold standard treatment for OSAS, especially in severe cases [12]. The effectiveness of CPAP is undoubted but many patients do not tolerate its use, reported rates of nonadherence ranges from 46% to 83%, that is the reason why alternative treatments are needed [4]. Septoplasty, tongue reduction, uvulopalatopharyngoplasty, maxillomandibular advancement and others surgery procedures can be other therapeutic strategies for OSA, although limited to particular cases. Oral appliances, such as mandibular advancement devices (MAD) and tongue-retaining devices, are definitely better tolerated by patients and can be an alternative for patients who do not tolerate CPAP. While tongue-retaining devices are not supported by a strong evidence [13], the use of MAD is considered a valid alternative in OSA patients, since it was demonstrated that it can markedly reduce the AHI and the oxygen desaturation index (ODI), improving patients' quality of life [14,15]. The other important aspect evaluated was about the limited side effects on temporo-mandibular joint (TMJ) function by use of MAD in 12.5–33% of these patients [16]. Other treatment options can be used to reduce obstructive sleep apnea, they include dietary weight loss or bariatric surgery in case of obese patients, reducing alcohol and sedative medications, eliminate the habit of smoking [17].

Some patients treated for OSA using CPAP therapy can reduce their obstructive sleep apnea, while developing or still showing central sleep apneas events. This is a disorder called TECSA, "treatment emergent central sleep apnea" [18] and it can be also defined as "complex sleep apnea syndrome", thanks to Gilmartin at al. who first described this kind of event in association with CPAP [19]. Several studies associated CPAP therapy and the emergence of TECSA [19–21], and surgical therapy seems also to be involved [22]. Only few studies described the link between the use of oral devices, specifically the mandibular advancement device and treatment emergent central sleep apnea. There are some case reports [23–25] reported the emergence of central sleep apneas in patients during treatment for obstructive apneas with MAD.

The aim of this cohort study was to evaluate the relationship between the use of mandibular advancement device and the emergent central sleep apnea on a larger number of patients with obstructive sleep apnea.

2. Materials and Methods

2.1. Study Population

A total of 56 patients (46 men and 10 women; mean age of 30.5 ± 8.7 years) were enrolled in this retrospective study. They all had a diagnosis of OSA confirmed by cardiorespiratory polysomnography (PSG) and were treated with night-time MAD therapy at the Department of Orthodontics, University of Foggia. Consent to participate in the study was signed by each of the enrolled participants. The declaration of Helsinki and its subsequent revisions have been respected in this research and all the operations performed have been approved by the Ethical Committee of the University of Foggia (Approval no. 43/CE/2019). All researchers participated in the study each addressing one aspect of the research.

Inclusion criteria were: age above 20 years old, body mass index (BMI) lower than 34 kg/m^2, diagnosis of OSA confirmed by PSG, and no Temporo-mandibular disease (TMD) MAD therapy for OSA treatment.

Exclusion criteria were: smoking habit, Temporo-mandibular disease (TMD), consumption of medications for neurological disorders or a history of cervical head trauma, comorbidities such as arrhytmias, congenital heart disease, and stroke and heart failure or pulmonary diseases at the moment of the OSA diagnosis.

2.2. Methods and Parameters

A drug-induced sleep endoscopy (DISE) is a type of examination that involves endoscopic analysis of the upper airway in an unconscious state and is used to assess the structures involved in the obstruction and at what level it occurs [4]. DISE was performed before treatment (T0) in a sleep laboratory using a type 2 portable device (Embletta system X-100, Flaga, Reykjavik, Iceland), in every patient who received a split-night polysomnography (SN-PSG) that recorded electroencephalograms, electro-oculograms, electromyograms, pulse oximetry channels, abdominal respiratory effort bands, body position sensors, nasal cannulas and oral thermistor. Three months after treatment using a fully customizable MAD (Protrusor®, nonrusso+®, Dr Giuseppe Burlon, Belluno, Italy) (T1) another SN-PSG was performed (Figure 1). This device is composed of two resin splints connected by two threaded titanium bars with two titanium screw each, which act as the protrusive component of the device. The advancement of the mandible was chosen for every patient after an initial period of titration. First was set an advancement at 70% of the total using an intraoral gauge (Occlusion®, nonrusso+®, Dr Giuseppe Burlon, Belluno, Italy) then every 15 days the mandibular protrusion was fixed by 1–2 mm increments until reaching the most comfortable and therapeutic position. The following parameters were extracted from PSG records and collected for further analysis: AHI, ODI, the number of obstructive (OSA), central (CSA) and mixed apnea during sleep recording.

(**a**) (**b**) (**c**)

Figure 1. Mandibular Advancement Device. (**a**) left lateral view, (**b**) frontal view, (**c**) right lateral view.

2.3. Statistical Analysis

Descriptive statistics were computed for all the variables. Data distribution was evaluated through a Shapiro-Wilk normality test and using histograms, boxplots and Q-Q plots. The presence of statistically significant differences between the T1 and the T0 measurements for all the variables was assessed using a paired samples *t*-test or a Wilcoxon signed rank test, depending on the type of data distribution. In order to evaluate the presence of factors that could explain the onset or the persistence of CSA, the sample was divided into two groups, one composed of subjects showing the outbreak or the increase of CSA events from T0 to T1, and another composed of subjects that never showed or discontinued CSA events; next, an independent samples *t*-test or a Mann-Whitney U-test was used to compare OSA, AHI, ODI, age, BMI, and the amount of mandibular advancement between the two groups. The three outlier cases were included in the latter analysis. The statistical analysis was performed using SPSS software (SPSS Statistics for Windows, Version 20.0., IBM Corp, Armonk, NY, USA). Type I error was set as $p = 0.05$.

A power analysis (G*Power 3.1.9.2, Franz Faul, Universitat Kiel, Kiel, Germany) revealed that to detect a large effect size of 0.5 with a Wilcoxon signed rank test, considering an alpha of 0.05 and a power of 0.95, 47 subjects would be needed [26].

3. Results

All the patients of the sample had a first diagnostic PSG (T0) with obstructive respiratory events per hour of sleep, AHI, >5 all of which reduced in the second PSG after three months (T1).

The examination of the boxplots and Q-Q plots revealed that, concerning the CSA values, three cases were outliers. Because those cases showed a number of central apnea events very high at T1 of 125, 62, and 176, well above the mean of the whole samples that was equal to 10.94 (Table 1). It is clear that the presence of those subjects clearly influenced the significance of the results. Those three outliers were removed from the analysis, but this allowed the authors to guess that these subjects defined as "outliers" would be critical to the purpose of the study.

Table 1. PSG parameters of outliers before and after treatment. CSA parameters at T0 and T1 are written in bold.

PSG DATA	CASE n.12	CASE n.25	CASE n.41
OSA T0	84	81	42
OSA T1	5	23	6
CSA T0	**23**	**63**	**42**
CSAT1	**125**	**176**	**62**
MIXED T0	135	64	11
MIXED T1	9	12	2
AHI T0	40.8	32.4	15.3
AHI T1	23.5	31.3	10.6
ODI T0	41.9	23.1	8.5
ODI T1	20.2	22.3	2.8

Figure 2 describes the statistical results for OSA, CSA, MIXED apnea, AHI and ODI data from T0 to T1 without the three outliers and shows the mean values of the variables OSA, CSA, MIXED apnea, AHI and ODI at T0 and at T1. Statistical comparison of mean values for the parameters considered was significant for all values, with a p value < 0.001 for OSA, MIXED apnea, AHI and ODI and a p value < 0.05 for CSA.

The number of OSA events was markedly reduced from T0 to T1. Central and mixed apnea values showed an important reduction from T0 to T1. MAD therapy showed also an important effectiveness in reducing AHI and ODI. All these changes were statistically significant.

The Authors divided the sample in two different groups: those who neither developed nor increased the number of central apneas during treatment (40 patients) (Figure 3) and those who as a result of the use of MAD developed or increased the number of central apneas (16 patients including 3 outliers) (Figure 4). Figure 3 describes variables at T0 in patients without developing o increasing CSA. Mean value in OSA is 113.05 while SD is 77.16, mean advancement is 79.74 while SD is 15.28. Mean AHI value is 24.48 while SD is 12.17, mean ODI value is 18.04 and SD is 9.41. Mean age and mean BMI are, respectively, 56.62 and 27.27 while SD are, respectively, 12.71 and 2.74. Figure 4 describes variables in patients who developed or increased the number of CSA at T0. In this case mean OSA is 106.27 and SD is 97.27. Mean mandibular advancement is 50.67 while SD is 16.78. Mean AHI and mean ODI are, respectively, 25.22 and 20.39 and SD are, respectively, 13,09 and 16.23. Mean age and mean BMI are, respectively, 54.07 and 26.72 and SD are, respectively, 11.56 and 2.76.

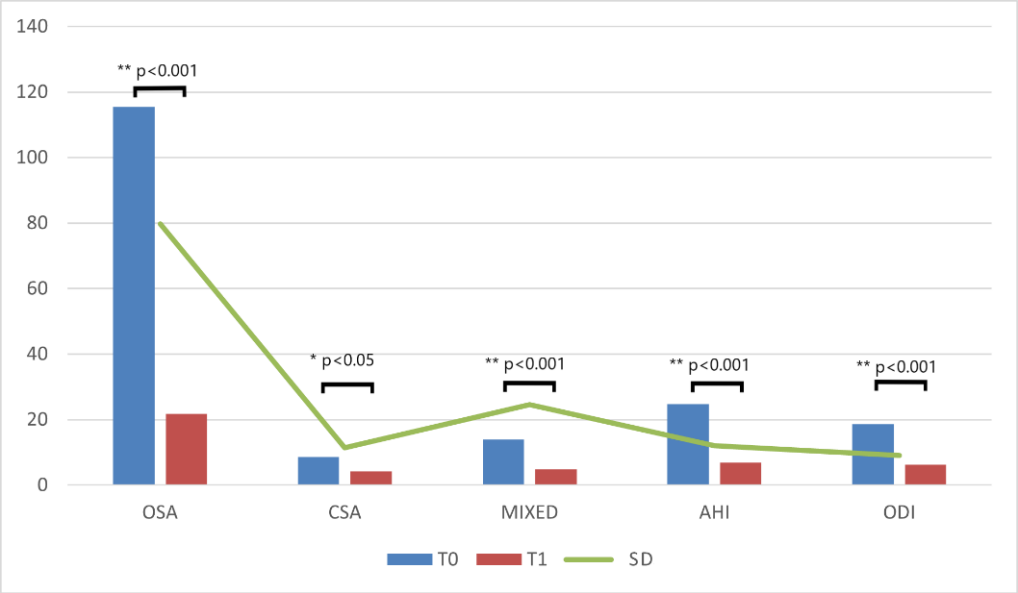

Figure 2. Descriptive statistics and statistical comparison of PSG parameters before (TO) and after (T1) treatment, standard deviation (SD) of the mean value of the difference between T1 and T0 for all the parameters (* $p < 0.05$; ** $p < 0.01$).

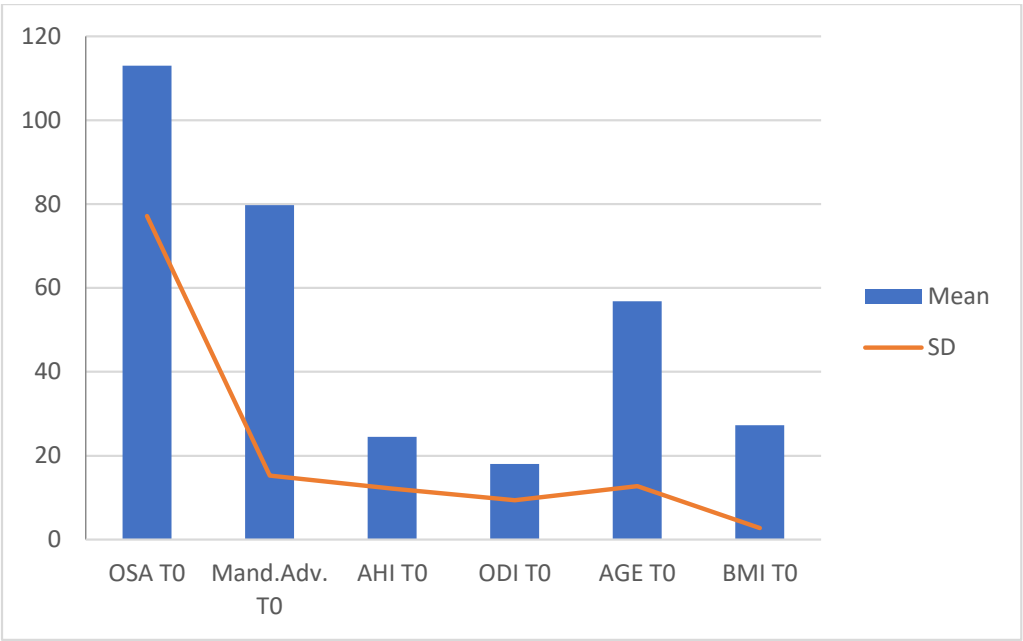

Figure 3. Descriptive variables table in patients who neither developed nor increased the number of CSA.

When comparing the two groups there were no statistically significant difference for the studied variables. According to data distribution were used for two different statistical tests to analyze variables at T0: the *t*-test has been used for AGE and BMI variables while the Mann-Whitney U test has been used for OSA, Mandibular advancement, AHI and ODI variables.

Analyzing and evaluating the medical records of the outlier patients a mild hypertension was found in 2 of the 3 patients and only one of them had a history of opioid drugs use not taken at the time of diagnosis.

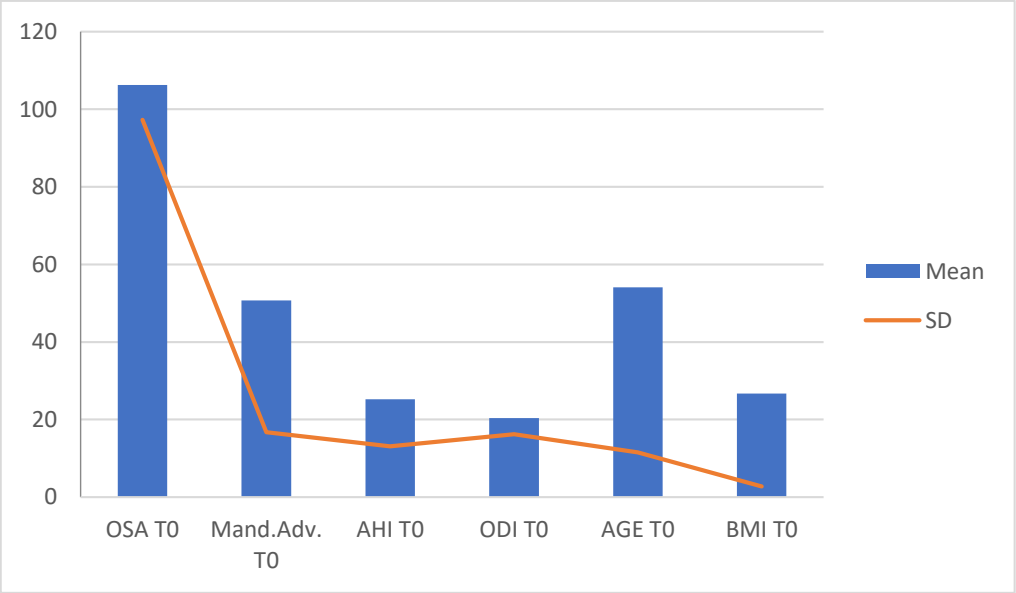

Figure 4. Descriptive variables table in patients who developed or increased the number of CSA.

4. Discussion

The International Classification of Sleep Disorders-Third Edition (ICSD-3) has included treatment emergent central sleep apnea as a syndrome that requires OSAS diagnosis followed by significant resolution of the obstructive apnea and emergence or persistence of central apnea during PSG after CPAP treatment, not related with other comorbidities [27]. Although currently the classification does not include the development of treatment emergent central sleep apnea with other kind of therapies these are to date increasingly used. A clinical review by Berger et al. reveals that TECSA is a rare phenomenon that can occur with all alternative OSA treatments, mandibular advancement devices, all types of surgery including tracheostomy, maxillomandibular advancement surgery and hypoglossus nerve stimulator [28]. In the scientific literature an important variability in TECSA's prevalence is reported, ranging from 5% to 20%. One of the reasons for this large range is the lack of established diagnostic criteria or protocols that define it and the different methodologies used in the studies [18]. Another reason can be the different use of split-night or full-night CPAP; split night studies seem to report a higher prevalence that may be connected to the lower capacity to evaluate breathing disorder's severity [29]. Nigam et al. reported an increased risk of developing TECSA in male and older patients who had a high baseline AHI: patients with a higher AHI had an increased risk of developing TECSA compared to patients with a lower index [20]. An increased CAI (central apnea index) can also predict TECSA emergence, so the presence of a high number of central apneas at diagnosis is a possible risk factor. Lower body mass index and chronic opiate use can also predict TECSA according to an article review by Zhang et al. [18]. Cardiovascular issues are common in patients with TECSA such as congestive heart failure, ischemic heart disease, coronary artery disease and hypertension [20], even if Kuzniar et al. reported that one-third of patients do not have any pathology before the sleep test and still develop TECSA [30]. According to Rao et al. risk factors are male gender, hypertension and history of cardiac disease, coronary artery disease, stroke, congestive heart failure, increasing age, higher baseline apnea-hypopnea index and central apnea index and opioid use [31]. Another matter reported by Nigam et al. is that TECSA can occur at any CPAP setting, according to their results there are no statistically significant differences between patients with TECSA and those without TECSA in CPAP settings [20]. The results of the present study do not confirm the observation reported by the previous literature regarding CPAP therapy; indeed, no differences in terms of OSA, ODI, AHI, age, BMI and amount of mandibular advancement

were observed between those subjects that showed CSA events compared to those who did not show signs of CSA. Moreover, central sleep apnea values showed a significant decrease from T0 to T1 when the whole sample—excluding the three outlier cases—was evaluated.

The American Academy of Sleep Medicine define TECSA or "complex sleep apnea" as a disorder characterized by persistence or emergence of central apneas with CPAP treatment while obstructive sleep apneas are mainly resolved. Treatment emergent central sleep apnea, according to some studies, is a transitory condition that could resolve after some weeks of treatment with CPAP [32,33]. According to Zeineddine et al. it would be preferable to divide subjects undergoing treatment with CPAP and that have TECSA into two different categories: on the one hand those who develop central apneas following treatment on the other hand those who have persistence of central apneas with treatment, this would be an indication of failure of therapy and the need to switch to another type of treatment [34]. An original study noted that analyzing a group of patients being treated for obstructive sleep apnea with PAP therapy, at one and 13 weeks after treatment, those who presented treatment emergent central sleep apnea in the first week were 3.5% but they resolved it by the thirteenth week. TECSA persisted in only a quarter of the affected patients, who had the highest rates of dropping out therapy. This means that in many cases treatment emergent apnea is a condition that resolves spontaneously and when TECSA persists there is a need to change therapy [35]. A study conducted by Dernaika et al. noticed an unsolicited resolution of central sleep apnea activity with CPAP in 86% of sample in 2–3 months, defining TECSA as a transient disorder and self-limited [36]. The pathophysiological mechanisms leading to the development of TECSA are not yet fully understood. Certainly, there are two factors that conceptually underlie the development of this pathology: low apnea threshold and high loop gain (LG). LG can be defined as a feedback mechanism consisting of the controller gain, that is the change in ventilation induced by a change in PaCO2 level and the plant gain, the ability of the lungs and respiratory muscles to increase ventilation. A high loop gain means increased response to small chemical stimuli leading to ventilatory instability [18]. According to Muza et al. in ventilatory control, controller gain stands for chemoreflex sensitivity, plant gain is the measurement of variation in blood gases and the delay gain is defined by circulatory delay and blending gases between blood and various tissues. Another important factor to evaluate is that LG is not a fixed value but tends to change continuously in an unstable situation as in the case of an OSA patient with obstructed breathing. This can occur as a result of many variables: blood gas change, lung volume, negative intra-thoracic pressure, respiratory muscle activity, and airway resistance [37]. Men are more likely to develop central treatment apnea than women because they have statistically a higher loop gain [31]. Apnoeic threshold (AT) is the individual's PaCO2 value below which a central apnea will occur, meaning that if the PaCO2 level falls below this threshold, spontaneous respiratory activity will stop [38]. Arousals from sleep is determined by a neuromechanical drive associated with ventilatory effort that immediately precedes arousal from sleep. When breathing decreases during an apnoeic event, the carbon dioxide associated with respiratory- efforts increases. Subjects with a higher threshold are better able to tolerate increases in respiratory drive [32]. A low AT threshold is one of the pathophysiological mechanisms of OSAs. In patients with obstructive sleep apnea, electroencephalographic micro-wakings are often observed on polysomnography. These patients are characterized by an instability of the respiratory system and control due to a low AT threshold, leading to frequent transitions from sleep to arousal and vice versa. When ventilation increases, subsequent ventilatory overshoot may cause the PaCO2 level to fall below AT, resulting in the onset of central apnea [18].

There is a correlation between central sleep apnea and OSA as far as some patients being treated for obstructive sleep apnea. Continuous positive airway pressure increase lung volume and improve CO2 damping (reducing plant gain) [33]. The prevalence of treatment emergent central sleep apnea development associated with C-PAP use is highly variable in the literature, this ranges from 5% to 20% [21]. In accordance with this Liu et al. defined the emergence of central apnea using CPAP therapy really variable but older

patients and higher AHI seem to be two risk factors that increase the probability to develop TECSA [35]. TECSA has also been associated with surgery, occasionally described after the surgical treatment of OSAS, in particular with tracheostomy and maxillomandibular advancement [39]. CPAP and oral appliances can intermittently decrease PaCO2 level to a value below the AT. An over-titration of CPAP may have an impact on CSA occurrence: the activation of stretch receptors of the lungs could inhibit the central respiratory output thanks to vagal nerve fibers, leading to the development of a central apnea [18]. Although there is very limited evidence about the use of MAD has also been reported to be associated to the development of TECSA, although only in case reports.

In fact, the authors believe that there is little literature on the subject and further studies are necessary to investigate the association between mandibular advancement device and treatment emergent central sleep apnea. Mohan et al. have described a case report of a 69-year-old man with OSA and without central apnea at the diagnosis, who refused CPAP because of claustrophobia and accepted MAD as therapy. After three months the patient developed treatment emergent central apnea showing an AHI that was not significantly different from baseline, but 49% of the respiratory events were central. He was monitored for an additional year and then another PSG with his MAD was repeated. The polysomnography showed very mild residual OSA with complete resolution of his central events [17].

Kuźniar et al. have reported two patients with complex sleep apnea after treatment with an oral appliance. Case one was a 59-year-old man who showed severe OSA at polysomnography with severe obstructive sleep apnea and central sleep apnea. He firstly accepted CPAP therapy but subsequently the patient refused it as a treatment option due to claustrophobia and inability to adjust to the mask and chose to pursue an alternative therapy with a mandibular advancement device. The use of MAD resolved obstructive apnea worsening central ones. Case two is a 57-year-old man with a diagnosis of mild OSA who increased the number of central apneas reducing the number of obstructive ones [15] Gindre et al. described a case report of a patient of 50-years-old with moderate OSAS who did not reduce obstructive apneas and increased exponentially central apnea during treatment by a bi-bloc MA device. [23] A development of central sleep apnea has also been noted by Avidan et al. in a 32-year-old gentleman who initially accepted CPAP as treatment but after few months he refused it describing it too cumbersome to travel with it and then he was advised to an oral device. After 2 months of therapy PSG recorded a higher AHI and a large development of central apneas [40]. Mohan et al. described a case of treatment emergent central sleep apnea that had a spontaneous resolution [25].

In conclusion, the results of this research suggest that oral devices are a valid alternative therapy to treat OSA patients, being able to significantly reduce all the altered parameters: AHI, ODI, OSA, CSA and MIXED apnea. In Some isolated cases MAD may contribute, as well as CPAP or surgery, to the development of treatment emergent sleep apnea. However, the current study had several limitations due the limited sample-size of evaluated patients, to the limited observation time and to the lack of homogeneity in the sample group between male and female subjects. However, these data could be used to sample a larger group and to put the findings more in context.

5. Conclusions

In accordance with the previous scientific literature, this study demonstrated the effectiveness of mandibular advancement treatment; after three months of MAD therapy all the studied indexes (OSA, CSA, AHI, ODI) showed a statistically significant improvement. Some patients in the sample, however, developed central apneas and when dividing the sample into two groups based on the presence or absence of central apnea, no statistically significant difference in baseline OSA, AHI, ODI, age, BMI, and mandibular advancement was observed. Three cases of the sample showed an abnormally high number of CSA after three months of MAD treatment. Therefore, as for the use of CPAP related with the

development of TECSA, so the definition of TECSA reported by ICSD-3, should refer to the phenomenon not only in CPAP treatment but in all kinds of therapies for OSA.

Further research is needed in order to investigate pathophysiological mechanisms leading to the development of TECSA and the factors that could predict the onset of central sleep apnea in patients treated with MAD and especially analyzing hypertension as a possible risk factor in the development of TECSA.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

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