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Original Article

The Evaluation of APAP Titration Results: Good Titration Versus TECSA and Unacceptable Titration

Sezgi Şahin Duyar[1], Deniz Çelik[1], Selma Fırat[2]

[1]Deparment of Pulmonology, University of Health Sciences Atatürk Chest Diseases and Thoracic Surgery Education and Research Hospital, Ankara, Turkey
[2]Sleep Disorders Center, University of Health Sciences Atatürk Chest Diseases and Thoracic Surgery Education and Research Hospital, Ankara, Turkey

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Abstract

OBJECTIVE: The first choice for treatment in severe and moderate obstructive sleep apnea syndrome (OSAS) is positive airway pressure (PAP) devices. However, despite proper titration, respiratory events may persist, while central respiratory events may increase or emerge for some patients. The primary aim of this study is to compare the clinical, demographic, and polysomnographic features of patients with different titration results.

MATERIAL AND METHODS: The patients who underwent automatic PAP (APAP) titration with the nasal mask in our clinic due to moderate or severe OSAS in 2017 were included in the study. The clinical, demographic, and polysomnographic characteristics of patients with successful (good) titration, "unacceptable" APAP titration, and treatment-emergent central apnea syndrome (TECSA), were recorded retrospectively and evaluated comparatively with statistical methods.

RESULTS: Out of 942 titration tests with APAP, 37 patients were diagnosed as TECSA (3.9%), while unacceptable (unsuccessful) titration results were seen only in 20 patients (2.1%). For the successful titration group, 44 consecutive patients were recruited. In the TECSA group, the central apnea index and minimum SpO_2 were higher during the diagnostic polysomnography (PSG). In the unacceptable titration group, the baseline minimum SpO_2 was lower. The lower sleep efficiency, lower stage N3 sleep, and longer rapid eye movement (REM) and sleep latencies were observed in the TECSA group during the titration test. The diagnostic accuracy of PAP device recordings was found to be moderate (kappa value: 0.533).

CONCLUSION: The baseline polysomnographic features, including higher central apnea index and minimum SpO_2, may raise suspicion for titration failures for which a laboratory-based titration can be scheduled.

KEYWORDS: APAP titration, obstructive sleep apnea syndrome, treatment-emergent central apnea syndrome, titration failure
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INTRODUCTION

The treatment of obstructive sleep apnea syndrome (OSAS) depends on eliminating respiratory-related events by the optimal pressure adjustment for a positive airway pressure (PAP) device. The standard PAP titration is utilized manually by a sleep technician. Additionally, automatic PAP (APAP) devices are used as an alternative to manual titration.[1] Despite the efforts in optimizing the pressure, the obstructive respiratory events persist or transform into central respiratory events for some patients. The emergence of central respiratory events after the treatment of OSAS is known as treatment-emergent central sleep apnea (TECSA), which was listed as one of the central sleep apnea syndromes in the International Classification of Sleep Disorders—third edition.[2] It is usually seen with the initiation or during the follow-up of the continuous positive airway pressure (CPAP) treatment.[3] The other therapeutic approaches, including dental appliances and surgical procedures for OSAS, may also lead to TECSA.[4-6] A high loop gain and lowering the level of arterial carbon dioxide below the apneic threshold are the main pathophysiologic mechanisms proposed for the emergence of central respiratory events after treatment of OSAS.[7,8] Recent studies have indicated some clinical and polysomnographic contributors related to the titration process, medical history, and the polysomnographic characteristics of the patients. When compared to OSAS, older age, male gender predominancy, and lower excessive daytime sleepiness were reported as characteristics for TECSA by some researchers. It was also claimed that the diagnostic polysomnography (PSG) had some differences for TECSA, like higher indexes for central apnea, mixed apnea, and arousals.[6,7]

The recognition of the patients who are prone to TECSA or unacceptable titration results may utilize the diagnostic and therapeutic approach. The main objective of this study was to discover the clinical predictors of TECSA. The secondary end point was to evaluate the diagnostic accuracy of the reports from the auto-adjusting positive airway pressure (APAP) devices.

Corresponding author: Sezgi Şahin Duyar, e-mail: drsezgisahin@gmail.com

MATERIAL AND METHODS

Patients and Study Design

In 2017, APAP titration with a nasal mask was performed for 1042 moderate/severe OSAS patients (age > 18 years) in our clinic. After 100 tests (89 insufficient sleep efficiency, 11 recording errors) 165 were excluded from the evaluation, and titration was successful with APAP in 877 patients (93.1%). Out of the remaining 65 patients, obstructive respiratory events persisted to the level of unacceptable (unsuccessful) titration in 20 patients (2.1%), while they were substituted with central respiratory events in 45 patients. The 37 patients (3.9%) in whom more than 50% of respiratory events were central type, were included in the TECSA group. Out of the 877 patients, a sample of 44 patients within the same age range was selected consecutively. The flowchart of the study design is shown in Figure 1.

If RDI (respiratory disturbance index) of the titration test was scored as >10/h or a reduction in RDI by 75% from baseline in severe OSA patients was not achieved, the results of the titration were graded as unacceptable.[9]

For the treatment-emergent central apnea, we used the diagnostic criteria of the International Classification of Sleep Disorders—third edition, in which the term was defined as central RDI > 5 events/hour comprising > 50% of events.[2]

The clinical and demographical characteristics including age, gender, body mass index (BMI), sleep-related symptoms, smoking status, comorbidities, and scores on the Epworth sleepiness scale (ESS), and the results of pulmonary function tests (PFT) were noted for both of the groups. The data were obtained by retrospective review of patients' medical files.

The study protocol was approved by the institutional review board of University of Health Sciences Atatürk Chest Diseases and Thoracic Surgery Education and Research Hospital (decision no: 606 decision date: August 9, 2018). The study design was retrospective, therefore ethical committee approval was not required. All procedures performed in this study were upheld ethical standards of the institutional review board and the 1964 Declaration of Helsinki and its later amendments. Only the records of patients, who signed the informed consent for the use of their data, were analyzed.

MAIN POINTS:

- The clinical, demographic, and polysomnographic characteristics of patients with treatment-emergent central apnea syndrome (TECSA) were compared with successful (good) titration and "unacceptable" automatic PAP (APAP) titration. Male gender and lower BMI emerged as the possible risk factors for TECSA.The patients with TECSA seemed to have higher central apnea index not only in titration test but also in diagnostic polysomnography (PSG).
- Minimum Spo_2 level during diagnostic and titration PSGs can be used to estimate titration results.
- The titration PSG of the patients with TECSA showed some characteristics of high loop gain phenotype, including lower sleep efficiency, lower stage N3 sleep, and longer REM and sleep latencies.
- The interrater concordance between the recordings obtained from the APAP device and the manual scoring of the titration test were found to be lower in the titration failure group.

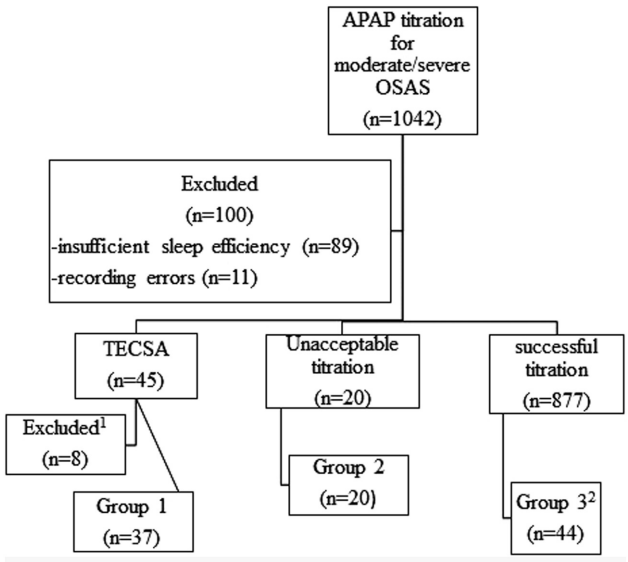

Figure 1. Flowchart showing the study design. [1]The patients in whom less than 50% of respiratory events were central type, were excluded. [2]The group 3 comprises age-matched consecutive patients.

Measurements

Diagnostic nocturnal polysomnography (NSPG) and APAP titration with simultaneous NSPG were performed using the digital systems in our sleep center (Neuron Spectrum EEG and EP Neurophysiological System Version 1.6.9.6, Neurosoft, Russia and Compumedics Voyager digital Imaging E-series System, Compumedics Ltd, Melbourne, Victoria, Australia). Standard PSG montages including 4 channels of the electroencephalogram, 2 channels of the electrooculogram, 1 channel of chin electromyogram, the thermistor, airflow, inductive plethysmography for thoracoabdominal motion, electrocardiography, and arterial oxygen saturation by finger pulse oximetry (SpO_2), were used. All records of EEG and respiratory events were manually scored according to the criteria of the American Academy of Sleep Medicine (AASM) Scoring Manual Version 2.2[10] by a sleep specialist certified by the Sleep Society in Turkey.

APAP titration was held by different trademarks of the devices available in our laboratory (ResMed, AutoSet T, Sydney, Australia, Weinmann Somnobalance-e Hamburg, Germany, or Phillips Respironics REMstar Auto A-flex, Murrysville, USA). The residual RDI was defined as the number of respiratory events per hour manually scored on PSG during the titration test. The available data from the recordings of the devices including RDI, maximum pressure, titrated pressure of 95th percentile (P95), and the presence of excessive leak were also reviewed and statistically compared between the groups. Excessive mask leak is defined as the time spent with a large leak is ≥ 1.5% for the Weinmann devices, the P95 of nonintentional leakage is ≥ 11 L/min for the ResMed devices, and the 90th percentile of total leakage is ≥ 45 L/min for the Phillips devices.[11]

Table 1. Demographic and Clinical Characteristics*

	TECSA (Group 1), *n* = 37	Unacceptable Titration (Group 2), *n* = 20	Successful Titration (Group 3), *n* = 44	*P*
Age (years)	53.5 ± 14.5	55.5 ± 13.1	51.2 ± 11.3	.444
Gender (male, %)	34 (91.9)	12 (60)	32 (72.7)	**.015**
BMI (kg/m^2)	28.4 (25.8-30.3)	31.2 (26-36.1)	30.4 (29.1-32.6)	**.011**
Smoking status (never smoked, %)	21 (56.8)	13 (65)	24 (57.1)	.808
Packages/year	25.9 ± 15.7	16.9 ± 13.1	23.7 ± 8	.325
Comorbidities				
Hypertension	18 (48.6)	10 (50)	11(25.6)	.057
Diabetes mellitus	5 (13.5)	4 (20)	7 (16.3)	.814
COPD-Asthma	4 (10.8)	1 (5)	10 (23.3)	.112
Symptoms				
Snoring	35 (94.6)	17 (85)	42 (97.7)	.141
EDS	17 (45.9)	12 (60)	28 (65.1)	.215
Witnessed apnea	26 (70.3)	17 (85)	34 (79.1)	.412
ESS score	8 (3-12)	10 (5.8-13.8)	9 (5-12)	.182
PFT				
FVC (L)	3.9 ± 1	3.3 ± 1.3	3.7 ± 1.1	.213
FVC%	92.5 ± 15.7	85.8 ± 18.4	90.8 ± 17.8	.389
FEV1(L)	3.2 ± 0.9	2.9 ± 1.1	3 ± 0.9	.355
FEV1%	94.7 ± 17.2	90.5 ± 20.3	90.4 ± 20.7	.599
FEV1/FVC	82.4 ± 5.9	85.7 ± 5.3	81.2 ± 7.5	**.048**
The prescription rate of PAP therapy (%)	19 (51.4)	13 (65)	44 (100)	**<.001**

*The values represented as mean ± standard deviation, median (25th-75th percentile), or *n* (%).
BMI, body mass index; COPD, chronic obstructive pulmonary disease; EDS, excessive daytime sleepiness; ESS, Epworth sleepiness scale; FEV1, forced expiratory volume during the first second; FVC, forced vital capacity; PAP, positive airway pressure; PFT, pulmonary function test; SD, standard derivation; TECSA, treatment-emergent central sleep apnea.

Statistical Analysis

We used The Statistical Package for Social Sciences version 21.0 software (IBM Corp.; Armonk, NY, USA) for all analyses, and overall significance was taken as a *P*-value of <.05. First, the normality tests were performed for all of the variables, using histograms, the ratio of the standard deviation to mean, and the Shapiro–Wilk test. The normally distributed variables were presented as mean ± SD. The non-normally distributed variables were presented as median (25th-75th percentile). Nominal variables were presented as number and percentage of cases. After homogeneity of variances was confirmed by the Levene's test, one-way ANOVA was used to compare the means. When an overall significance was observed, a pairwise post-hoc analysis was performed via Tukey's test. Kruskal–Wallis tests were conducted to compare the medians of the non-normally distributed variables. The Mann–Whitney *U*-test was then performed to find the pairwise differences. A chi-square test was used to examine the difference between groups for categorical variables. According to Bonferroni correction to adjust the pairwise comparisons of 3 groups, $P < .017$ was considered to show a statistically significant result. The changes in mean and minimum SpO_2 during titration were compared by the Wilcoxon test. The similarity between the results obtained by manual scoring and the recordings of the APAP device were analyzed by the kappa test.

RESULTS

When the data from 37 patients with TECSA (group 1), 20 patients with unacceptable titration (group 2), and 44 patients with successful titration (group 3) were compared, a statistically significant difference was observed in gender distribution, BMI, and FEV1/FVC. The pairwise comparisons revealed that TECSA was observed more frequently in men than in the unacceptable titration group ($P = .011$) and the patients with TECSA had lower BMI than those in the successful titration group ($P = .002$). For FEV1/FVC, the pairwise analysis did not yield a significant difference between the groups. The other demographic and clinical features including age, smoking status, presence of comorbidities or sleep-related symptoms, and the results of PFT were found to be statistically the same between the groups. As expected, the ratio of prescription for PAP treatment was higher in group 3, but no difference was observed between groups 1 and 2 ($P = .32$) (Table1).

The evaluation of data from diagnostic NPSG revealed that central RDI and the level of minimum and mean Spo2% were statistically different between the groups (Table 2). Pairwise analysis elucidated that the significance in mean SpO_2 originated from the difference between groups 2 and 3 ($P = .006$).

Table 2. Polysomnographic Characteristics*

	TECSA (Group 1), *n* = 37	Unacceptable Titration (Group 2), *n* = 20	Successful Titration (Group 3), *n* = 44	*P*
Total recording time	470 (457.1-478.5)	471.7 (452.4-477.9)	477.1 (462.9-486.7)	.056
TST	363.5 (308.0-410.5)	339.8 (297.6-390.6)	475.5 (329-419)	.239
WASO	66.5 (34.0-104.0)	84.4 (52.6-130.2)	59.6 (27.7-107.4)	.378
Sleep efficiency (%)	77.6 ± 13.1	78.2 ± 12.5	78.7 ± 11	.917
Sleep latency (min)	22.5 (11-36)	9.8 (7.3-22.5)	16.5 (7-29.5)	.123[3]
REM latency(min)	110.5 (81.5-166.5)	107.5 (84.4-179.6)	108.5 (75-174)	.928
Stage N1 (%)	6.4 (2.6-14.4)	6.2 (1.9-14.9)	8.2 (3-16.2)	.681
Stage N2 (%)	62 ± 8.8	61.2 ± 10.6	62.9 ± 8.3	.771
Stage N3 (%)	14.5 ± 7.5	16.7 ± 10.7	14.2 ± 7.1	.533
REM (%)	15 ± 5.6	13.5 ± 7.2	13.4 ± 5.3	.449
RDI	36.8 (28.9-58.4)	41.4 (31.6-56)	36.2 (24.6-48)	.346
Central RDI	2.3 (0.6-7.2)	0.4 (0-1.0)	0.2 (0-1.3)	**<.001**
Obstructive RDI	34.7 (25.4-49.3)	41 (31.7-58)	34.9 (24.4-47.2)	.380
REM RDI	40.4 ± 22	54.4 ± 23	43.9 ± 20.1	.063
Non-REM RDI	34.9 (25.1-59.8)	39.5 (28.8-55)	32.7 (24.1-47.5)	.289
Supine (%)	54.3 (25.4-91.7)	44.8 (20.2-71.7)	64 (28.4-100)	.297
Supine RDI	50.4(31.3-62.1)	57.2 (38.3-75.4)	36.6 (26.3-64.6)	.153
Non-supine RDI	22.1 (16.1-49.9)	27.8 (16.8-38.8)	18.5 (0-36.3)	.230
Mean SpO_2	91.8 ± 2	90.4 ± 2.6	92.3 ± 2.5	**.009**
Minimum SpO_2	79 (72-81)	71.5 (61.5-76.8)	77 (72.3-81.8)	**.006**

*The values represented as mean ± standard deviation, median (25th-75thpercentile), or *n* (%).
REM, rapid eye movement; RDI, respiratory disturbance index; SD, standard deviation; SpO_2, arterial oxygen saturation by finger pulse oximetry; TECSA, treatment-emergent central sleep apnea; TST, total sleep time; WASO, wake after sleep onset.

However, for minimum SpO_2, the difference was also significant between groups 1 and 2 (*P* = .003) (Figure 2). Central RDI was higher in the TECSA group than in groups 2 and 3 (Figure 3).

However, we could not find any statistically significant difference for the other polysomnographic parameters including wake time after sleep onset (WASO), percentages of the sleep stages, sleep latency, REM latency, sleep efficiency, or RDI (Table2).

As expected, according to the polysomnographic data obtained during titration, central RDI was higher in the TECSA group and obstructive RDI was higher in group 2. Obstructive RDI was also higher in the TECSA group when compared to the successful titration group (*P* = .012). The unacceptable titration group

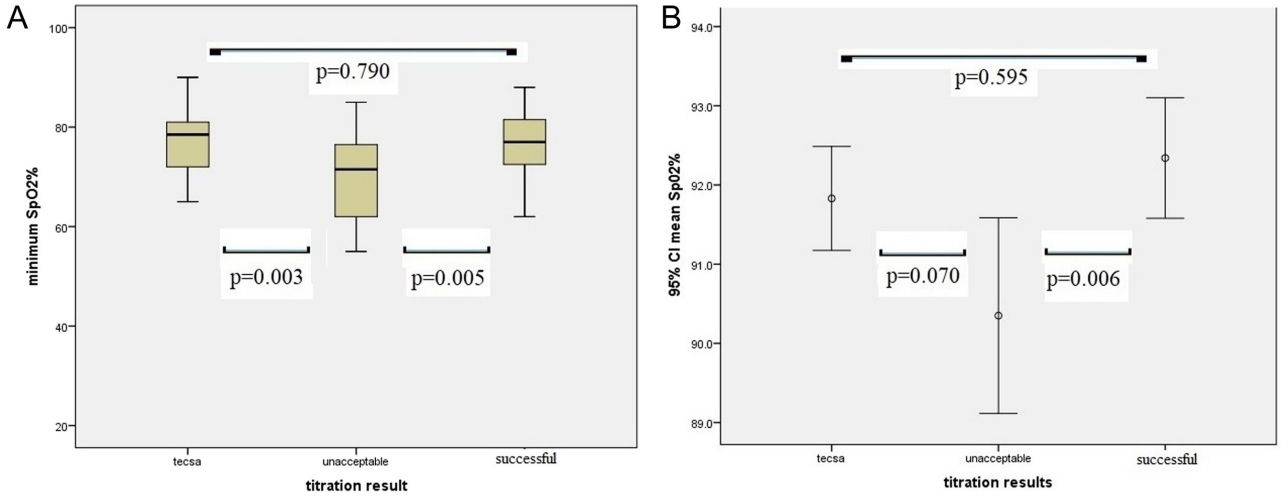

Figure 2. (A) Boxplot for minimum SpO_2 showing the significant differences between the groups. (B) Error bar for mean SpO_2 showing that the difference is significant between unacceptable titration and successful titration.

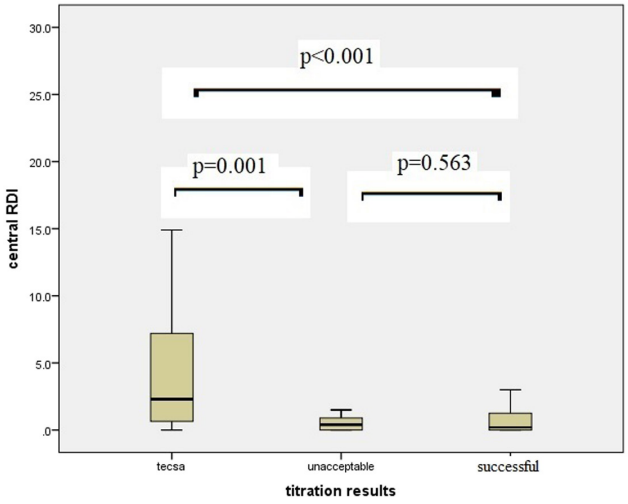

Figure 3. Boxplot showing that TECSA group has higher central RDI than both the unacceptable and successful titration groups.

presented with higher REM RDI whereas the TECSA group had the highest non-REM RDI. When compared to group 3, both REM RDI and non-REM RDI were higher for patients with TECSA ($P < .001$). Most of the residual respiratory events occurred during non-REM sleep stages for TECSA. When compared to group 2, the comparisons for REM RDI and non-REM RDI were statistically the same with TECSA ($P > .017$). The titration PSG revealed statistically different characteristics for the TECSA group, including higher stage N2% and REM latency, but lower stage N3%, sleep efficiency than group 3 (Figures 4 and 5). Although sleep latency during titration seemed to be statistically the same ($P = .065$), the median of sleep latency in the TECSA group was nearly 2-fold of group 2 ($P = .015$, Mann–Whitney *U*-test). Like diagnostic PSG results, the minimum and mean Spo2% during titration were also statistically different between the groups. However, the significance in mean SpO_2 during titration originated from the difference between groups 1 and 2 ($P = .013$). For minimum SpO_2, higher values were obtained for the successful group when compared to groups 1 and 2 ($P < .001$) (Table 3). A statistically significant change in the median of minimum SpO_2 (12%) was obtained in only the successful titration group ($P < .001$, Wilcoxon test). The median of mean SpO_2 during titration did not improve statistically from the baseline value obtained during diagnostic PSG in any of the groups ($P > .05$, Wilcoxon test).

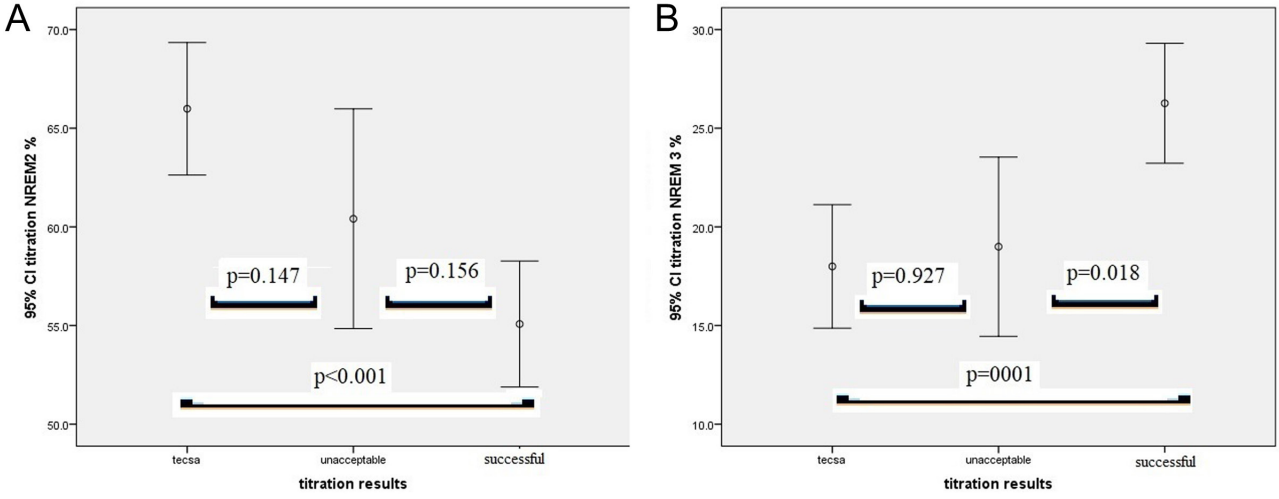

Figure 4. Error bars for stage N2% (A) and stage N3% (B) during titration showing that the difference is significant between TECSA and the successful titration group.

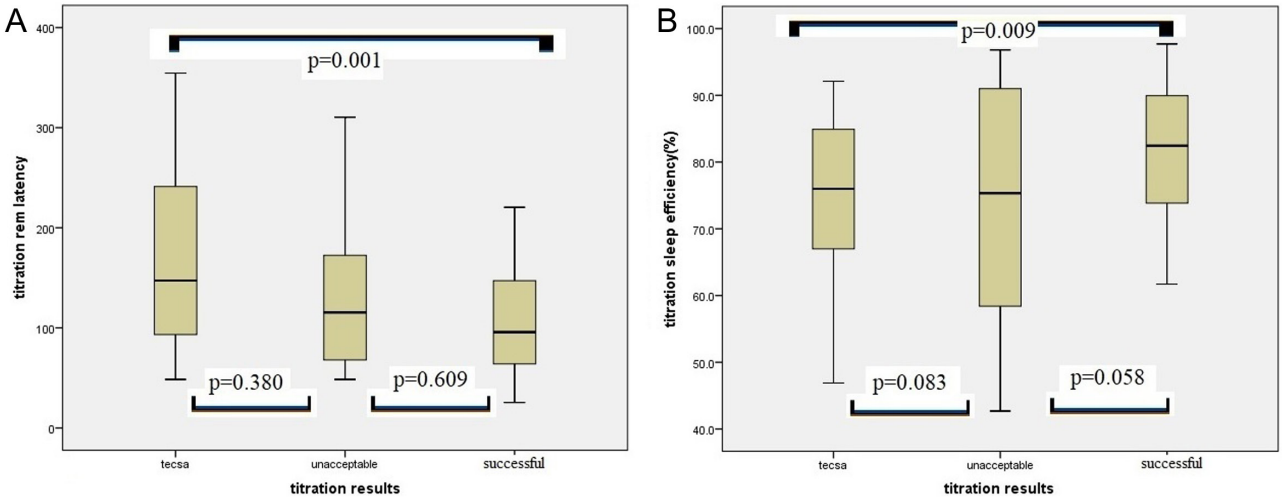

Figure 5. Boxplots for REM latency (min) (A) and sleep efficiency percent (B) during titration showing that the difference is significant between the TECSA and the successful titration groups.

Table 3. Polysomnographic Characteristics During Titration*

	TECSA (Group 1), *n* = 37	Unacceptable Titration (Group 2), *n* = 20	Successful Titration (Group 3), *n* = 44	*P*
Total recording time	472.2 (462.6-480.5)	480.7 (457.1-491.4)	668.7 (458.2-475.2)	.197
TST	349.7 ± 66.9	342.9 ± 88.2	369.8 ± 54.5	.234
WASO	89.5 (48.0-132.8)	135.7 (49.9-192.2)	82.5 (33.6-127.9)	.055
Sleep efficiency (%)	76 (64.8-85.2)	75.4 (57.2-91.3)	82.5 (73.6-90.2)	**.020**
Sleep latency (min)	12.0 (7.5-28.0)	6.8 (4.5-12.8)	10.3 (6.1-22)	.065
REM latency (min)	147.3 (92.4-241.6)	115.5 (58.3-241.5)	95.8 (63.3-149.8)	**.004**
Stage N1 (%)	2.3 (1.1-4)	2.5 (1-6)	1.7 (0.5-2.7)	.091
Stage N2 (%)	66 ± 10.1	60.4 ± 12	55.1 ± 10.5	**<.001**
Stage N3 (%)	18 ± 9.4	19 ± 9.7	26.3 ± 10	**<.001**
REM (%)	11 (9.3-16.1)	13.8 (10.8-20.1)	15.1 (10.4-20.8)	.081
RDI	16.4 (14.4-21.3)	15.2 (13.3-28.9)	3 (1.4-5.5)	<.001
Central RDI	14.8 (9.7-17.1)	1.3 (0.6-2.5)	1.1 (0.4-2.4)	**<.001**
Obstructive RDI	3.1 (0.5-6.8)	14.1 (11.9-26.3)	1.3 (0.2-2.5)	**<.001**
REM RDI	8 (5.2-15)	17.8 (8.6-24.6)	1.9 (0-3.9)	**<.001**
Non-REM RDI	17.3 (15.3-21.3)	16.1 (12.4-30.7)	2.6 (1.1-5.5)	**<.001**
Mean SpO_2	94 (91.8-94)	92 (89-93)	92 (91-93)	**.026**
Minimum SpO_2	80.5 (76.3-81.8)	74.5 (70-79.3)	89 (88-90)	**<.001**

*The values represented as mean ± standard deviation, median (25th-75th percentile), or *n* (%).
REM, rapid eye movement; RDI, respiratory disturbance index; SD, standard derivation; SpO_2, arterial oxygen saturation by finger pulse oximetry; TECSA, treatment-emergent central sleep apnea; TST, total sleep time; WASO, wake after sleep onset.

The data obtained from the recordings of APAP devices were also analyzed (Table 4). In the TECSA group, P95 reached higher values than group 3 ($P = .002$). Then, we recoded the maximum pressure data into a dichotomous variable, such as the tests with maximum pressure≥15 cmH_2O and < 15 cmH_2O. Despite the overall significance ($P = .026$) and the higher ratios of the tests that reached levels ≥15 cmH_2O in groups 1 and 2, the pairwise analysis did not result in any statistically significant difference between the groups ($P > .017$).

As shown in Table 5, the agreement between the results obtained by manual scoring and the recordings of the APAP device was analyzed by the kappa test ($P < .001$). The agreement between manual scoring and the device recordings is 76.3%. Since the kappa value is 0.533, with some exceptions, it can be said that the results are mostly similar, and have a medium level of agreement. The ratio of the interrater agreement was higher in the successful group than in the other group (88.6% vs. 66%).

DISCUSSION

This study presents important results for the clinical, demographic, and polysomnographic characteristics of TECSA. The comparisons between all possible titration results revealed the polysomnographic parameter to be used in estimating titration results. As a secondary end point, our results underline the importance of manual scoring in titration failure.

The heterogeneity of sleep apnea covers a larger spectrum which can be outlined by enhanced phenotyping. The clinical (e.g., OSAS with excessive daytime sleepiness) polysomnographic (non-REM-dominant,

Table 4. The Recordings of PAP Devices During Titration*

	TECSA (Group 1), *n* = 37	Unacceptable Titration (Group 2), *n* = 20	Successful Titration (Group 3), *n* = 44	*P*
RDI	17.4 (11.5-23.8) (*n* = 34)	10.9 (3.5-18.6) (*n* = 17)	5.3 (2.9-7.7) (*n* = 44)	**<.001**
Maximum pressure	11.9 (9.5-15.3) (*n* = 20)	9.9 (9.5-17.1) (*n* = 8)	10 (8.8-12.4) (*n* = 29)	.065
Max pressure >15 cmH_2O (%)	8 (30.8)	4 (40)	2 (6.7)	**.026**
P95	10.9 (9-13.6), (*n* = 26)	10.4 (8.6-15.3) (*n* = 10)	8.6 (7.7-10.7) (*n* = 33)	**.006**
Excessive mask leak (%)	17 (50) (*n* = 34)	10 (62.5) (*n* = 16)	15 (34.1) (*n* = 44)	.109

*The values represented as median (25th-75th percentile), or *n* (%).
PAP, positive airway pressure; P95, titrated pressure of 95th percentile; RDI, respiratory disturbance index; SD, standard deviation; TECSA, treatment-emergent central sleep apnea.

Table 5. The Comparison of the Results Obtained from PAP Device Recordings Versus Titration PSG

		PAP Device Recordings		
		TECSA/Unacceptable Titration (*n* = 40), *n* (%)	**Successful Titration (*n* = 57), *n* (%)**	***P***
Manuel titration	TECSA/unacceptable titration (*n* = 53)	35 (66)	18 (34)	<.001
	Successful titration (*n* = 44)	5 (11.4)	39 (88.6)	

PAP, positive airway pressure; PSG, polysomnography; TECSA, treatment-emergent central sleep apnea.

REM-dominant OSA), and pathophysiologic (e.g., high loop gain, low arousal threshold) phenotypes have been described in the recent studies.[12,13] The phenotyping of sleep apnea promises better diagnostic and therapeutic approaches. Our study may contribute to determining the characteristics of phenotypes that do not respond to PAP treatment and the phenotype of high loop gain.

Treatment-emergent central sleep apnea is an important clinical phenomenon that has been linked to ventilatory instability due to high loop gain.[7,8] Out of 942 assessable titrations held in our sleep clinic in 2017, 3.9% of the titrations, mostly in male patients, were evaluated as TECSA. Likewise, the prevalence of TECSA was reported between 1.6% and 20% in CPAP-treated patients.[3] The wide range in prevalence can be associated with sample size, split vs full-night studies, and the average age of the population included in the previous studies.[14,15] Male gender, older age, lower BMI, and cardiac comorbidities were the parameters claimed to increase the likelihood of having TECSA.[8,16,17] The studies reported these results by comparing patients with TECSA and OSAS. In this study, we compared the characteristics of the TECSA group with patients who had persistent obstructive respiratory events and respond to APAP titration. We aimed to outline the differences between the patients with the emergence of central respiratory events (TECSA group) and the patients with high residual RDI of obstructive events (unacceptable titration). Except for male predominance and lower BMI, the other clinical and demographic parameters including age, BMI, comorbidities (diabetes mellitus, hypertension, and obstructive respiratory diseases), smoking history, sleep-related symptoms, ESS scores, and PFT were statistically similar between the groups. Only 51.4% of the TECSA group completed the tests and accepted the prescription of PAP therapy, whereas 65% of the other group had reached out to PAP therapy. The difference in prescription rates is 13.6%, which is statistically the same.

The evaluation of the diagnostic PSGs reveals that the central apnea index on baseline PSG is also higher than the other groups (2 vs. 0.4, P = .001). Diagnostic PSG with higher kappa test specifically increasing during non-REM supine sleep can also be used in discriminating TECSA from OSAS.[8,16-20] Despite the nonsignificant results according to the Bonferroni correction, REM RDI was also lower than the unacceptable titration group in TECSA (P = .03). Non-REM predominancy and higher central apnea indexes can be considered as clues for high loop gain. However, RDI and WASO as a indicators of arousals were similar for all the groups during diagnostic PSGs.

Titration PSG also outlined some differences featuring the TECSA group to have lower sleep efficiency and the ratio of slow-wave sleep (stage N3%) and longer REM latency than the successful group. When these 2 groups were compared, both REM RDI and non-REM RDI were also found to be higher for the TECSA group. Nevertheless, in the TECSA group, most of the respiratory events during titration seemed to occur in non-REM stages. The sleep latency of the TECSA group during the titration test was also found to be longer, but overall statistical significance could not be shown (12 min vs. 6.8 min, respectively P = .015) The relationship between ventilatory instability and anxiety disorders, especially panic attacks, has been a point of interest. PSG in anxiety disorders shows increased sleep latency.[21,22] Regarding the longer sleep latency in the TECSA group of our study, we recommend that the anxiety level of patients with TECSA must be further investigated.

Oxygenation levels during diagnostic and titration PSG showed different patterns. The highest mean SpO_2 during both tests was observed in the successful titration group, whereas the highest minimum SpO_2 during diagnostic PSG belonged to the TECSA group. The baseline mean SpO_2 levels were similar between groups 1 and 3. The only significant improvement in oxygenation during titration was obtained in the minimum SpO_2 level of the successful titration group. The increase in minimum SpO_2 was 12% in this group, while it was only 1.5% in the TECSA group. As stated in the study of Lehman et al.[8] these results supported that the respiratory instability in TECSA would not seem to be driven by baseline desaturations. However, the higher residue of respiratory events may block the improvement in oxygenation during titration.

The records derived from the PAP devices (Table 4) showed no difference between the groups in the mean values of the leak and maximum pressure. Like the study of Dernaika et al.,[23] higher P95 pressure was reached for patients with TECSA than for those in group 3. Nevertheless, P95 did not differ between groups 1 and 2 (P = .82). Despite the higher residual RDI in the TECSA group, the ratio of tests which reached maximum pressure ≥ 15 cmH_2O was similar in the pairwise analysis of the groups. Due to overall significance (P = .026), it must not be ignored that the successful titration group had the highest ratio of the patients for whom the maximum pressure capped below 15 cmH_2O. It can be recommended that the patients who need less than 15 cmH_2O for the recovery of respiratory events are more likely to be successfully titrated with APAP devices. The patients who seem to need less than 15 cmH_2O can be determined by a mathematical equation to predict PAP, and these patients can be auto-titrated.

Our results showed that the recordings of the APAP device had a moderate interrater concordance with the manual scoring (Table 5, kappa value: 0.533). Because of the lack of correct sleep time and variabilities in detecting respiratory events, automatic devices may misdiagnose the titration failure as successful titration. The ratio of the interrater agreement was higher in the successful group than in the other group (88.6% vs. 66%). This finding underlines the importance of the follow-up of the patients who are advised to use PAP devices after home testing for titration. Despite good adherence to the PAP device, a patient with this scenario who lacks clinical improvement should undergo a laboratory-based titration test for differential diagnosis. Although readjustment of the apneic threshold in a few weeks or months of the therapy yields spontaneous remission in most of the patients with TECSA, one-third of the patients remain persistent.[24,25] The patients with persistent TECSA may benefit from advanced modalities like bilevel PAP with backup rate and adaptive servo-ventilation.[26] Furthermore, a new category of delayed-TECSA patients was defined as the cases who would present with TECSA a few months after the initial exposure to PAP therapy.[20] Further research is needed to delineate the clinical or polysomnographic characteristics of the patients exhibiting spontaneous remission and persistent or delayed TECSA.

As to the limitations of this study, in our cohort, we did not have any patients with congestive heart failure. Different trademarked brands of APAP devices were used which could complicate the interpretation of the data derived from devices. Moreover, due to retrospective design, we could not reach out to all the data of APAP devices.

CONCLUSION

Diagnostic PSG can offer some clues like non-REM predominancy and higher central RDI, in determining patients who are prone to TECSA. The lower level of baseline minimum SpO_2 can be used for predicting nonacceptable titration results in which advance modalities of PAP devices may be needed. The lower sleep efficiency, lower stage N3 sleep, and longer REM and sleep latencies observed in the TECSA group during titration may be consequences of ventilatory instability and anxiety which are compatible with the high loop gain phenotype.

Ethics Committee Approval: The study protocol was approved by the institutional review board of our education and research hospital (decision no: 606 decision date:9/8/2018). The study design was retrospective so ethical committee approval was not required.

Informed Consent: Written informed consent was obtained from the patients who agreed on the usage of their records for educational and scientific purposes.

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