Sleep Medicine Reviews 58 (2021) 101513

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

Treatment-emergent central sleep apnea associated with non-positive airway pressure therapies in obstructive sleep apnea patients: A systematic review

Mathieu Berger [a, *], Geoffroy Solelhac [a], Christian Horvath [b], Raphael Heinzer [a], Anne-Kathrin Brill [b]

[a] Center for Investigation and Research in Sleep (CIRS), Lausanne University Hospital (CHUV), University of Lausanne, Lausanne, Switzerland
[b] Department of Pulmonary Medicine, Inselspital, Bern University Hospital and University of Bern, Bern, Switzerland

ARTICLE INFO

Article history:
Received 25 November 2020
Received in revised form
26 April 2021
Accepted 28 May 2021
Available online 5 June 2021

Keywords:
Obstructive sleep apnea
Central sleep apnea
Complex sleep apnea
Treatment-emergent central sleep apnea

SUMMARY

This systematic review summarizes the prevalence of treatment-emergent central sleep apnea (TECSA) occurring with therapies other than positive airway pressure (PAP) for the management of obstructive sleep apnea (OSA). We describe its natural course as well as the proposed underlying pathophysiological mechanisms and the clinical management of affected patients. A systematic search of PubMed, Embase, Web of science, and the Cochrane Library was performed until June 2020. Eighteen studies (n = 284 patients) were included. TECSA was observed in 31 patients with the use of four different medical devices (mandibular advancement device, hypoglossal nerve stimulation, tongue stabilizing device and nasal expiratory PAP) and after three different types of surgical treatments (tracheostomy, maxillofacial surgery and oro-nasal surgery). Due to the paucity of data available, it was not possible to establish a clear prevalence rate of TECSA for each alternative treatment. After the initiation of non-PAP treatments, a systematic reassessment of the treatment efficacy with follow-up sleep studies will be helpful to identify TECSA. A spontaneous resolution over time was described as well as a persistence of TECSA. In this case, treatment should focus on patients' specific underlying pathophysiology. Overall, the limited current literature suggests that this phenomenon is rare (<4%).

Introduction

Treatment-emergent central sleep apnea (TECSA) is a well-known phenomenon occurring in obstructive sleep apnea (OSA) patients upon application of positive airway pressure (PAP). In the largest study so far, the prevalence was 6.5% for CPAP-related TECSA [1]. A literature review confirmed this data with an aggregate prevalence of 8% [2], but also showed that prevalence may vary from 1.6% to 20.3% [3,4] depending on the applied inclusion criteria for comorbidities, titration protocols, and geographical settings.

Usually, TECSA is characterized by persistence or emergence of central apneas on exposure to PAP devices without a backup rate while the obstructive respiratory events that were noted during the prior diagnostic sleep study have resolved. In addition, central sleep apnea (CSA) should not be better explained by another disorder causing CSA syndrome.

Already in the 1980s, a PAP-independent nature of TECSA has been observed after tracheostomy in patients with severe OSA or "hypersomnia sleep apnea" as the disease was still called at that time [5,6]. With the subsequent great success of continuous positive airway pressure (CPAP) as first line treatment for OSA, research and reports on TECSA initially focused on this treatment modality and in 2014 TECSA was officially incorporated in the International Classification of Sleep Disorders – Third edition (ICSD-3) [7]. Although mentioned in the ICSD-3 chapter on TECSA, the definition does not include the occurrence of central apneas in OSA patients when restoring upper airway patency using other treatment modalities. Yet, alternative treatment modalities to CPAP are increasingly used in clinical practice and first reports on TECSA occurring with the use of devices such as mandibular advancement devices (MAD) have been published already more than a decade ago [8,9].

* Corresponding author. Centre d'Investigation et de Recherche sur le Sommeil (CIRS), Centre Hospitalier Universitaire Vaudois (CHUV), Rue de Bugnon 46, 1011, Lausanne, Switzerland.
E-mail address: mathieu.berger@chuv.ch (M. Berger).

https://doi.org/10.1016/j.smrv.2021.101513

List of abbreviations

AHI	Apnea-hypopnea index
ASV	Adaptive servoventilation
CAI	Central apnea index
CMAI	Central and mixed apnea index
CPAP	Continuous positive airway pressure
CSR	Cheyne-Stokes respiration
HNS	Hypoglossal nerve stimulator
ICSD-3	International Classification of Sleep Disorders – Third edition
MAD	Mandibular advancement device
MeSH	Medical subject headings
MMA	Maxillomandibular advancement
NOS	Newcastle–Ottawa Scale
OSA	Obstructive sleep apnea
PAP	Positive airway pressure
PSG	Polysomnography
TECSA	Treatment-emergent central sleep apnea
TPCSA	Treatment persistent central sleep apnea

However, the prevalence of the phenomenon with non-PAP treatment modalities remains largely unknown.

With this systematic review, we aimed to investigate the prevalence of TECSA occurring with alternative therapies to PAP for the treatment of OSA and to describe its natural course as well as the underlying pathophysiological mechanisms and the clinical management of affected patients.

Methods

This systematic review was prospectively registered in PROSPERO (CRD42020149067).

Identification of studies

A systematic search of electronic databases including PubMed, Embase, Web of science, and the Cochrane Library was performed from inception through August 29, 2019. An update search was performed on June 30, 2020. The search included MeSH terms, keywords and phrases in various combinations. The following syntax was used as search strategy in the different electronic databases (["Sleep Apnea, Central" (MeSH)] AND [treatment-emergent) OR (treatment) OR (emergent") OR (complex)]. In addition, we performed backward and forward citation-chaining of relevant literature from the reference lists of identified reports and articles to identify other pertinent articles that might have been missed during the electronic database search. No language limits were imposed at the time of screening the articles. Selection of relevant studies was performed in duplicate by at least two independent investigators using Covidence tool [10] and any disagreement was resolved by consensus with a third reviewer.

Inclusion and exclusion criteria

The inclusion criteria were the following: 1) human participants of both sex; 2) participants aged 16 years or older; 3) OSA assessed by polysomnography (PSG) or respiratory polygraphy at baseline; 4) treatment with another treatment modality than PAP (e.g., surgery, other devices); 5) a new or established diagnosis of TECSA with this alternative treatment by PSG or polygraphy without time restrictions. We included reports fulfilling the ICSD-3 TECSA definition and those with TECSA defined close to this definition only if they provided enough data to allow comparison to the other studies. Missing subclassification of hypopneas as obstructive or central were tolerated.

Articles were excluded if 1) patients did not receive any treatment for OSA; 2) there was no detailed information on the alternative treatment; 3) there was no detailed description of the follow-up.

Data extraction and management

Data extraction was performed in duplicate (MB and AKB) from all eligible studies with a standardized pre-specified data collection sheet. The following aggregate data were collected: first author's name, year of publication, number of participants, gender, age, body mass index (BMI), comorbidities, apnea-hypopnea index (AHI) at baseline and at follow-up, central apnea index (CAI) at baseline and at follow-up, prior OSA treatment if any, type of treatment that led to TECSA, symptoms with non-PAP treatment, frequency of TECSA, time and number of follow-up visit, delay until onset of TECSA, further evolution, and applied countermeasures. Any disagreements between the investigators were resolved by research team consensus.

Quality assessment

For the included cohort studies we applied the Newcastle–Ottawa Scale (NOS) [11]. Given that there are still no validated tools to assess the risk of bias of case reports and case series, we utilized an adapted form of the NOS with items that were appropriate for this systematic review [12]. In the adapted version NOS items that related to comparability and adjustment were removed and those that focused on selection, representativeness of cases, and ascertainment of outcome and exposure were retained. This resulted in five criteria in the form of questions with a binary response (yes/no), whether the item was suggestive of bias or not. The quality of the report was considered as good (low risk of bias) when all five criteria were fulfilled, as moderate when four criteria were fulfilled and poor (high risk of bias) when three or fewer were fulfilled. Disagreement between the reviewers was resolved through research team consensus.

Results

Study selection

The schematic presentation of the study selection using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines is depicted in Fig. 1:

(i.) Identification: A total of 982 studies were generated from the database searches (Pubmed: 419 studies, Embase: 385 studies, Web of Science: 156 studies, and Cochrane Library: 22 studies), and additional seven were retrieved from backward and forward searching of reference lists of relevant articles and the final studies (ii.) Screening: after removal of duplicates 729 titles and abstracts were screened for eligibility; 692 did not meet basic eligibility criteria including one study without any abstract or full-text available [13] (iii.) Eligibility: 37 full-text articles were retrieved and further screened for eligibility. Nineteen studies were excluded for different reasons (iv.) Included: Eighteen studies were included in the present systematic review.

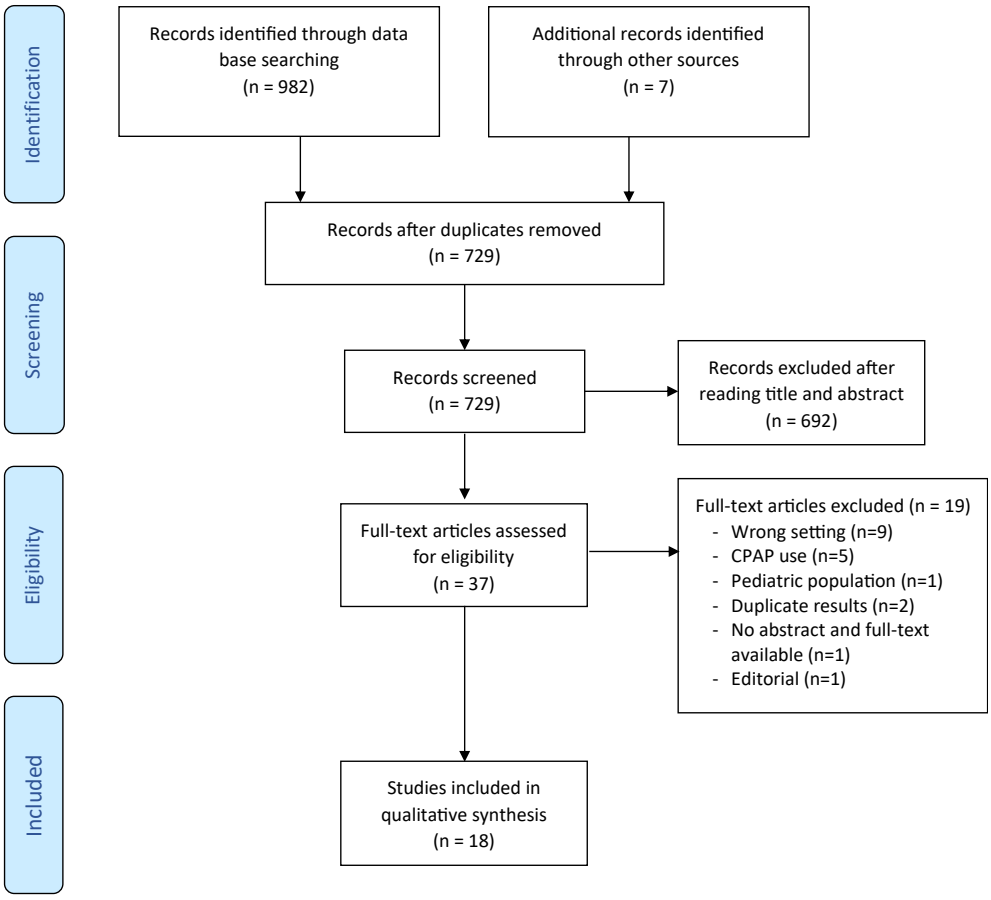

Fig. 1. Flow diagram of the literature search and study selection process.

Study characteristics

A summary of the included studies and applied treatment modalities is presented in Tables 1 and 2. The included studies were one prospective and one retrospective cohort, two case series, and 14 case studies comprising overall 284 patients, 31 out of them with TECSA. Studies included mostly men, middle-to-older-age patients who were overweight or obese. The majority of reports stems from sleep centers in North America (USA: 14 studies, Canada: two studies, France: one study, Italy: one study).

TECSA was described with the use of four different medical devices (MAD in four studies, hypoglossus nerve stimulator (HNS) in four studies, tongue stabilizing device and nasal expiratory PAP (nEPAP) in one study each, and after three different types of surgical treatments (tracheostomy in three studies, maxillofacial surgery in two studies and oro-nasal surgery in three studies). The risk of bias in the included case reports and case series was moderate or low (Table 3). The quality of the cohort studies was considered fair [14] or good [15].

Mandibular advancement devices

Our search identified four detailed publications comprising five male patients with OSA who developed TECSA with the use of a MAD (Table 1). Thus, no prevalence data was available for this treatment modality. The described patients had a mean age of 53.4 years (range 32–69) and a mean BMI of 31 kg/m^2. Comorbidities were variable but included atrial fibrillation in combination with arterial hypertension or a structural cardiac disease in all but the youngest patient. Left ventricular ejection fraction was reported as preserved in three patients. Medication included treatments for the comorbidities, but no drugs known to provoke CSA. The MADs were rigid bi-bloc devices in four cases and a soft mono-bloc device in one patient. Baseline OSA diagnostics showed a wide AHI range in the patients (ranging from 10.1 to 65 events/h) and an increase in the CAI with TECSA that fulfill the ICSD-3 definition for TECSA in all described cases. The interval between the start of the treatment with the MAD and the diagnosis of TECSA was not always described in detail. In three cases, the follow-up PSG revealing TECSA was performed two or three months after the initiation of the MAD treatment [8,9,16]. Despite the development of TECSA, two patients reported an improvement in symptoms, while there was no change in excessive daytime sleepiness in two other patients. The underlying mechanisms as proposed by the authors varied and included insufficient mandibular protrusion leading to persistent micro-arousals destabilizing nocturnal breathing [8], excessive mandibular protrusion [9], or high loop gain [17]. Noteworthy, a physiological spontaneous resolution was frequently observed over time [16].

This resulted in heterogeneous and individualized further treatment decisions ranging from the continuation of the MAD with a wait and see strategy and no change in the treatment, to a continued MAD use with an altered level of protrusion, alternating the MAD with CPAP, or a change to adaptive servoventilation (ASV).

Table 1
Characteristics of the included studies with devices.

Author, reference	OSA treatment	Study design	N	Prevalence TECSA	Male (%)	BMI [kg/m^2]	Age [y]	Co-morbidities	AHI BL [n/h]	AHI FU [n/h]	CAI BL [n/h]	CAI FU [n/h]	Symptoms with TECSA	Further management
Mandibular advancement device (MAD)														
Avidan 2006 [8]	MAD mono-bloc DeSRA®	Case study	1	n/a	1 (100%)	34	32	NR	10.1	25.7	0.4	17.8	Snoring ↓, EDS	NR, suggestion to increase protrusion
Gindre et al. 2006 [9]	MAD bi-bloc AMP™ 6 & 9 mm	Case study	1	n/a	1 (100%)	28	50	Afib, Hypothyreosis UPPP	27	6 mm: 19 9 mm: 52	0	6 mm: 2 9 mm: 34	6 mm: snoring ↓, unchanged EDS, 9 mm: snoring ↓, unchanged EDS	MAD at 6 mm alternating with CPAP
Kuzniar et al. 2011 [17]	MAD bi-bloc SomnoDent® 5.5 mm (pat 1) & 2.5 mm (pat 2)	Case study	2	n/a	2 (100%)	31.7 27.9	59 57	Afib, CAD, DM Afib, HTN, HypothyreosisLupus	65 17	67 33	7 1	51 12	Some improvement, EDS (ESS 19 → 13) Persistent EDS/fatigue (ESS 17 → 12)	ASV ASV
Mohan et al. 2016 [16]	MAD bi-bloc SomnoDent® 7.5 mm	Case study	1	n/a	1 (100%)	36.5	69	Afib, HTN, CAD, DM	16.2	14.9	0	7.3	Fatigue/poor sleep quality resolved	Spontaneous resolution PSG after 15 months
Hypoglossus nerve stimulator (HNS)														
Chan et al. 2018 [18]	HNS (+-+) 1.2 V	Case study	1	n/a	1 (100%)	31.4	61	Obesity	27 (REI)	24.7	NR	3.1 ± CSR	NR	Continued HNS with adapted configuration
Sarber et al. 2019 [19]	HNS 1.9 V	Case study	1	n/a	1 (100%)	27	60	AH, CKD, DM, bladder/kidney cancer, depression	22.6	83.8	0.3	78.9 + CSR	Improved EDS (ESS 11 → 7) and nocturnal breathing	HNS continued, repeat HNS titration with O2 is considered
Hong et al. 2019 [20]	HNS	Case study	1	n/a	1 (100%)	NR	76	Afib	18.6	NR	0.7	CSR	NR	HNS continued + Afib ablation + acetazolamide + eszopiclone
Patel et al. 2020 [15]	HNS (Inspire®)	Pro-spective cohort	141/5 TECSA	3.3%	94 (66.9%)	29.1 ± 3.9	61 ± 11	CCI ≥ 2 in 69% of patients	34.6 ± 19.0	8 ± 14 [0–94.7]	CMAI: 3.6 ± 7.2	CMAI: 1.3 ± 5.8	NR, entire cohort: improvement of EDS	Transient (n = 3), resolution with adapted HNS configuration (n = 1), persistent & BiPAP (n = 1)
Other devices														
Chopra et al. 2014 [22]	nEPAP (Provent®)	Case study	1	n/a	1 (100%)	24	72	mitral valve prolapse, septal deviation	18	48	0	11	Snoring and disturbed sleep continuity	CPAP (not tolerated), positional therapy
Alshhrani et al. 2019 [21]	Tongue stabilisation device (Aveo-TSD®)	Case study	1	n/a	1 (100%)	NR	70	DM, AT, CAD, depression, lat. TBC, NHL, hypercalcemia	25.5	71.1	1.1	39.2	NR (PSG was part of a research trial)	Positional therapy and evaluation for MAD

Abbreviations: AMP™: anterior mandibular positioning device; AFib: atrial fibrillation; BiPAP: bilevel positive airway pressure; BL: baseline; CAD: coronary arterial disease; CCI: Charleston comorbidity index; CKD: chronic kidney failure; CMAI: central and mixed apnea index; CPAP: continuous positive Airway pressure; CSR: Cheyne-Stokes respiration; DeSRA®: Dental Sleep Relief Appliance; DM: diabetes mellitus; EDS: Excessive daytime sleepiness; ESS: Epworth sleepiness scale; FU: follow-up; nEPAP: nasal end expiratory positive airway pressure; HNS: hypoglossus nerve stimulator; HTN: hypertension; MAD: mandibular advancement device; NHL: non Hodgkin lymphoma; NR = not reported; n/a = not applicable; pat: patient; REI: respiratory event index; lat. TBC: latent tuberculosis; UPPP: uvulopalatopharyngoplasty; *CAI >5/h [-]: range; y: years; n/h: number of events per hour of total sleep time; d: day; w: week; m: month; V: voltage.

Table 2
Characteristics of the included studies with surgeries.

Author, reference	OSA treatment	Study design	N	Prevalence TECSA	Male (%)	BMI [kg/m^2]	Age [y]	Comorbi-dities	AHI BL [n/h]	AHI FU [n/h]	CAI BL [n/h]	CAI FU [n/h]	Symptoms with TECSA	Further management
Maxillofacial surgery														
Corcoran et al. 2009 [24]	Maxillofacial surgery	Case study	1	n/a	1 (100%)	26	38	None	26	m3: 39 m6: 11.5	0	m3: 35 m6: 1.9	NR	Transient, spontaneous resolution
Goodday et al. 2019 [14]	Maxillofacial surgery	Retro-spective cohort	113/2 TECSA	1.8%*	84 (74%)	NR	44 ± 9 [17–68]	NR	47 ± 34	9 ± 7	CAI = 0 (n = 73) CAI >0 (n = 40), mean CAI 1.8	CAI = 0 (n = 59) CAI >0 (n = 54) CAI > 5 (n = 2)	NR	NR
Other surgeries														
Goldstein et al. 2012 [26]	Nasal surgery	Case study	1	n/a	1 (100%)	31.2	43	Sino-nasal congestion	5.8	30.2	0.2	24.5	EDS & sleep fragmentation	CPAP
Qamer et al. 2015 [27]	Complex ENT surgery	Case study	1	n/a	1 (100%)	29.2	50	None	18	35	0.2	18	EDS	NR
Testani et al. 2018 [25]	Complex ENT surgery	Case study	1	n/a	1 (100%)	27.8	49	None	48	d3: 71.2 d15: 21 d30: 14.6	4.6	d3: 64.1 d15: 10.4 d30: 4.7	None	Transient, spontaneous resolution
Tracheostomy														
Weitzmann et al. 1980 [5]	Tracheostomy	Case series	10/5 TECSA	50%*	10 (100%)	Over-weight	[39–47]	HTN, nasal pathology	110 ± 84	25 ± 33	4 ± 5	9 ± 9	EDS improved	Continued tracheostomy
Guilleminault& Cummiskey 1982 [6]	Tracheostomy	Case series	5	100%	5 (100%)	NR	46 [31–57]	HTN (3/5 patients)	65 ± 14	d2-3: 13 ± 3 w4-5: 7 ± 1 m3: 2 ± 2	1.1	d2-3: 30 ± 5 w4-5: 45 ± 10 m4-6: 0.8 ± 0.4	NR	Continued tracheostomy
Fletcher 1989 [23]	Tracheostomy	Case study	1	n/a	1 (100%)	Super-obese	NR	Snoring	114	50	0	50	EDS, dyspnea, right heart failure	Continued tracheostomy, temporary NIV, weight loss, diuretics

Abbreviations: NR = not reported, n/a = not applicable, ENT: Ear nose throat, EDS: Excessive daytime sleepiness, * CAI > 5/h, HTN: hypertension; BL: baseline; NIV: non-invasive ventilation; FU: follow-up; y: years; n/h: number of events per hour of total sleep time; d: day; w: week; m: month [-]: range.

Table 3
Risk of bias of the included case studies and case series.

First author, year	Q1		Q2		Q3		Q4		Q5		Risk of bias
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	
Tongue stabilizing device											
Alshhrani, 2019 [21]		x	x		x		x		x		moderate
Mandibular advancement device											
Avidan, 2006 [8]	x		x			x	x		x		moderate
Gindre, 2006 [9]	x		x		x		x		x		moderate
Kuzniar, 2011 [17]	x		x		x		x		x		low
Mohan, 2016 [16]	x		x		x		x		x		low
Nasal expiratory positive airway pressure											
Chopra, 2014 [22]	x		x		x		x		x		low
Hypoglossus nerve stimulator											
Chan, 2018 [18]	x		x		x		x		x		low
Hong, 2019 [20]	x		x		x		x		x		low
Sarber, 2019 [19]		x	x		x		x		x		moderate
Tracheostomy											
Weitzmann, 1980 [5]		x	x		x		x		x		moderate
Guilleminault, 1982 [6]		x	x		x		x		x		moderate
Fletcher, 1989 [23]	x		x			x	x		x		moderate
Maxillofacial surgery											
Corcoran, 2009 [24]	x		x		x		x		x		low
Other upper airway surgery											
Goldstein, 2012 [26]	x		x		x		x		x		low
Qamer, 2015 [27]	x		x		x		x		x		low
Testani, 2018 [25]		x	x		x		x		x		moderate
Total: 16 studies											Low risk: 8 Moderate risk: 8 High risk: 0

Detailed questions of the adapted Newcastle Ottawa scale: Q1. Did the patient(s) represent the whole case(s) of the medical center? Q2. Was the diagnosis correctly made? Q3.Were other important diagnoses excluded? Q4. Were all important data cited in the report? Q5. Was the outcome correctly assessed?

Hypoglossus nerve stimulator

The four identified reports from the USA included a prospective cohort study with 141 patients and three case reports on patients who developed TECSA with the use of an HNS (Table 2). The prevalence of TECSA in the monocentric prospective cohort was reported as 3.3% (n = 5 patients) [15]. The authors defined TECSA as patients with OSA (with a baseline CAI < 5 events/h) who demonstrated a central and mixed apnea index (CMAI) of ≥5 events/h and/or demonstrated Cheyne-Stokes respiration (CSR) becoming prominent or disruptive on HNS treatment, measured during the therapeutic device titration 6–8 weeks after device activation. As detailed data were reported mainly for the whole cohort, there is no full individual information available on patients who developed TECSA, but the authors reported a trend towards a lower BMI in affected patients. The Charlson Comorbidity index was ≥2 in 69% of all studied patients but details on the comorbidities, such as possible heart failure were not reported. All affected patients with an elevated CMAI after HNS activation were male and univariate analysis revealed that demographics, comorbid conditions, and device settings were not associated with an elevated postoperative CMAI. The only factor associated with CMAI ≥5 events/h on univariate analysis was an elevated postoperative AHI.

In the three case studies, all patients were male, aged between 60 and 76 years and two had comorbidities including chronic kidney disease, cardiac disease and atrial fibrillation [18–20]. Polysomnographies revealing TECSA were performed two to three months after the device implantation.

Pathophysiological considerations of the authors mainly focused on either an unresolved obstruction which may have led to microarousals and overshoot of $PaCO_2$ reduction below the apneic threshold during sleep or a demasking of an OSA or comorbidity related elevated loop gain. HNS was continued either with spontaneous resolution of central and mixed events over time or with advanced programming of the HNS device. In addition, the authors recommended a good control of co-morbidities including ablation of atrial fibrillation, and considered supplemental oxygen or the prescription of acetazolamide or eszopiclone. Only one of the eight affected patients had to discontinue HNS and was started on bilevel positive airway pressure therapy (BiPAP).

Other devices

One case report by Alshhrani et al. described TECSA with the use of a tongue protrusion device (aveoTSD®, Innovative Health Technologies, New Zeeland) in a male OSA patient with several comorbidities including coronary artery disease [21]. After an initially good response to the treatment with the tongue protrusion device, a split-night sleep study performed eight months later as part of a research trial revealed an insufficient control of sleep apnea with TECSA in the second half of the night with the device (Table 1). Although occurring in both supine and non-supine position, TECSA was more profound in the supine position, independently of sleep-stage effects. The patient's medications and medical conditions did not change during the follow-up. The authors did not bring forward any potential pathophysiological mechanisms.

Another case of TECSA was reported with a Provent® nEPAP device occurring in an elderly male patient with moderate OSA during a split-night PSG [22]. The patient had a cardiac dysfunction, a normal BMI and presented mixed (17/h) and central apnea events (11/h) with nEPAP in the second half of the night. Surprisingly, there was more REM sleep in the second half of the split-night (19.2% vs 2.6% in the first part of the diagnostic split night), which actually should have decreased the likelihood of CSA. The patient declined treatment and was not seen until 1 y after the sleep study. Then, CPAP was tried resulting in a CAI of 5 events/h, but also declined by the patient who was then advices to utilize positional therapy.

Tracheostomy

Three studies describing the occurrence of TECSA after tracheostomy were identified (Table 2). Since the case studies included only 16 patients, no real prevalence data was available.

Weitzmann et al. describe a homogeneous group of ten severe OSA patients with available PSG data acquired shortly after the tracheostomy (n = 9 in night 5, n = 1 in night 41) [5]. In parallel with a reduction of obstructive apnea events, seven patients presented a small increase of CAI, five of them with a post-tracheostomy CAI of more than 5 events/h meeting the definition of TECSA. The length of the central apneas was unchanged after tracheostomy compared to baseline.

A second case series by Guilleminault and Cummiskey described a progressive improvement of the apnea index after tracheostomy with a transient increase in CAI [6]. Patients underwent at least three follow-up PSGs showing a greatly increased CAI immediately after surgery, remaining elevated during four to five weeks post-surgery and then progressively normalizing over time while obstructive apneas remained low from the first postsurgical recording onwards.

The case report from 1989 by Fletcher describes a different type of TECSA [23]. With further weight gain, a male superobese OSA patient developed hypercapnic CSA and right heart failure with edema 4 years after tracheostomy. TECSA was reversed by a temporary application of mechanical ventilation over the tracheostomy and edema was treated with diuretics. Pathophysiological considerations by the author focus on alveolar hypoventilation induced by morbid obesity with chronic hypercarbia and hypoxemia predisposing to periodic breathing during sleep through changes in the respiratory controller.

Maxillofacial surgery

The emergence of TECSA after maxillofacial surgery was analyzed in a larger retrospective cohort including 113 patients as well as in a single case report. In the cohort study, PSGs were performed before maxillomandibular advancement (MMA) surgery and six months afterwards. Thirty-four patients of 73 (46%) without any central apneas before surgery experienced very mild and clinically insignificant new-onset central apneic events with a CAI range of 0.3–3 events/h and only one patient had a CAI of >5 events/h [14]. Of the 40 patients who presented with a few central apneic events before surgery, 39 experienced a decrease in their CAI from a mean CAI of 1.79 to 0.75 events/h, all having a CAI <5 events/h. Only one patient showed an increase in CAI from 0.2 to 11.2 events/h with a CSR pattern. This resulted in a TECSA prevalence of 1.8% in this cohort. The authors did not find any correlation of the postoperative development of central apneic events with male gender, patient age or increased pre-treatment AHI [14].

The case study from Corcoran et al. reported a more severe development of TECSA in a younger man that was evident in a PSG performed three months after MMA surgery [24]. The post-surgery CAI was 35 events/h and normalized spontaneously to 1.9 events/h in the follow-up PSG six months after the surgery. No information on sleeping position during the PSG was available. Despite being slightly overweight, the patient had no comorbidities. Pathophysiological aspects discussed by the authors focused on high loop gain, potential atmospheric glottis closing pressure with adaption of the ventilatory control to the new anatomical situation and reduced ventilatory load over time [24]. They proposed to wait at least six months after surgery before performing postoperative PSG.

Other surgery

The case study described by Testani et al. nicely documented the course of an early and transient TECSA in an otherwise healthy OSA patient who was moderately hypercapnic before upper-airway surgery including mucotomy, uvulopalatopharyngoplasty (UPPP) and partial epiglottectomy [25]. A series of PSGs performed three, 15 and 30 days after this surgery documented an early CAI increase that spontaneously and progressively decreased over time. The authors ruled out medication, neurologic, heart and respiratory disease. Therefore, they suggested TECSA to be triggered by a sudden normalization of nocturnal pCO_2 immediately after surgery in a patient with reduced chemosensitivity due to a long-term exposure to nocturnal hypercapnia. Another case study described TECSA after a nasal surgery for a mild OSA that was detected due to worsening symptoms with sleepiness and sleep fragmentation [26]. In this case, the authors noted an increase of RERAs in the follow-up PSG indicating a mixed pattern of insufficient relief of OSA and emergence of CSA with the surgery. Time in each sleeping position was not indicated in the initial diagnostic study, but the patient had position dependent sleep apnea in both PSGs. The authors discuss an increase in upper airway resistance and arousals as potential underlying mechanisms that contribute to ventilatory instability [26]. A similar case was presented in an abstract with TECSA being diagnosed about four months after UPPP, tonsillectomy and partial resection of the inferior turbinates bilaterally. TECSA also consisted of a mixed pattern of respiratory events with persistent obstructive hypopneas, but the majority of apneas and >50% of the AHI being central. Pathophysiological considerations of the authors focus on an augmented response to pCO2 and persistence of OSA, but the authors also indicate that the baseline and follow-up PSGs were performed at different institutions implying potential technical and interpretative differences [27].

Discussion

This systematic literature review is the first, to our knowledge, to investigate the prevalence and the pathophysiological mechanisms of TECSA with non-PAP therapies across several different treatment modalities. Eighteen studies were included that addressed TECSA occurring with four different medical devices (MAD, HNS, tongue stabilizing device and nEPAP), and three different types of surgical treatments (tracheostomy, maxillofacial surgery and oro-nasal surgery) to treat OSA. Although rare, our findings highlight that TECSA may occur with almost all common alternative treatment modalities and with heterogeneous pathophysiological mechanisms. Given the number of case reports and small case series included in this review, the true prevalence and clinical relevance of this phenomenon is still difficult to assess due to insufficient data for most treatment modalities.

Prevalence of TECSA with non-PAP therapies

The two cohort studies reported a 3.3% and 1.8% prevalence rate for HNS and maxillofacial surgery, respectively [14,15]. Surprisingly, while oral appliances are currently the most common alternative treatment for OSA management [28,29], we did not identify any cohort studies establishing a prevalence rate of TECSA with this kind of treatment. Still, the four identified case reports suggest that TECSA with MAD may occur. The prevalence rates for TECSA with HNS or after MMA surgery are lower than the prevalence reported with PAP therapy in the largest CPAP-study (6.5%) [1] and the systematic review of first time PAP-users (prevalence 8%, range 5.0–20.3% with 5.0–12.1% for full-night PSG and 6.5–20.3% for split-night PSG) [2]. A potential explanation for the observed

differences in prevalence compared to CPAP might be the usually longer interval with non-PAP treatments between the start of the intervention and follow-up diagnostic. Indeed, in-laboratory fixed pressure PAP titration will immediately reveal PAP-related TECSA. Similarly, PAP initiation in an outpatient setting with auto-CPAP devices provides a night-by-night analysis of residual events and may revealed PAP-related TECSA almost in real-time via telemonitoring [30].

By contrast, the PSGs after MMA or HNS were performed six months after surgery or six to eight weeks after the device activation, respectively. Therefore, with the exceptions of the few patients who were evaluated immediately after the initiation of a treatment, it seems more reasonable to compare TECSA induced by non-PAP alternatives to OSA patients who experience CSA with PAP over a prolonged period of time, i.e., treatment persistent central sleep apnea (TPCSA). Of interest, the prevalence data for PAP associated TPCSA on a long-term basis was 1.5% in the large CPAP-study [1] and ranged from 0.9 to 3.2% in a recent review [31] and although the authors consider this number to be potentially underestimated, it is closer to the prevalence data that we found for the cohort studies on HNS and MMA.

In our opinion, a potential underreporting of non-PAP related TECSA also warrants consideration as potential explanation for the scarce literature and low prevalence obtained, particularly with MADs as the most common second line treatment for OSA. One may argue that, although recommended, OSA is not always systematically re-assessed with a sleep study after the initiation of an alternative medical device or surgical treatment [29], as follow-up may only be symptom based and up to 20–25% of the patients do not keep regular appointments [32]. Limited resources to follow-up increasing numbers of OSA patients [33] by sleep centers [34] and the lack of device-generated data or telemonitoring options for most of the non-PAP alternatives also reduce the likelihood of a detection of TECSA.

Other potential explanations for a truly low prevalence of TECSA with the non-PAP alternatives compared to CPAP lay in the different pathophysiological mechanisms between the treatment modalities themselves. For instance, PAP-related TECSA may be promoted by an exaggerated CO_2 washout and activation of lung stretch receptors by increased tidal volumes that will inhibit the central respiratory motor output via Hering Breuer reflex [35]. These latter two mechanisms cannot be induced by the alternative treatment modalities. In addition, one could argue that there is a selection bias since patients receiving non-PAP treatment alternatives might have a lower AHI, a lower degree of comorbidities, and possibly a lower fraction of central apneas as compared to patients who receive CPAP.

Natural course

Since most of the studies included in the present systematic review were case reports or small case series, the timing of TECSA diagnostic could vary from few days up to several months after treatment initiation. Moreover, TECSA was not systematically re-assessed in the studies that we identified. Thus, it is difficult to characterize the natural evolution of TECSA for each non-PAP treatment. Nevertheless, a spontaneous resolution of early TECSA was nicely illustrated in several publications. This was notably the case over a period of several months in one case series after tracheostomy [6], after maxillofacial surgery [24] as well as in another case report over a period of 30 days after a complex ear-nose throat surgery [25]. Similar spontaneous resolution was found in some patients with HNS [15] or MAD [16]. However, these spontaneous resolutions are not systematic and other authors reported some cases with persistence of CSA over time [15]. Moreover, some authors proposed an immediate change of the treatment modality or a change of configuration of the device once TECSA is diagnosed, precluding to determine the natural course of TECSA with the non-PAP therapy.

Underlying pathophysiological mechanisms

The main pathophysiological mechanism of TECSA is certainly the dysregulated chemoreflex response to $PaCO_2$ of OSA patients newly treated. This mechanism was previously demonstrated with PAP-treatments and results showed that the ventilatory control adapts and normalizes within a period of a few weeks to several months [31,36,37]. Even though not all 31 retrieved TECSA cases in this review were thoroughly classified by the authors, we suggest that this mechanism also occurs with alternative treatments in susceptible patients, especially if reassessed early after the implementation of the alternative OSA treatment modality. In addition, some patients may suffer from comorbidities that favor an elevated loop gain, which consequently could favor TECSA once inspiratory flow limitation is relieved. Similarly, dynamic loop gain is elevated in supine position due to decreased supine lung volume [38] and thus may increase the likelihood of CSA in the follow-up studies if this body position is then preferred. However, only a few of the identified studies report body position during the sleep studies, thus we cannot confirm this hypothesis, but clinicians should consider the body position when TECSA is diagnosed.

In this review, we noted that several patients in the case studies suffered from cardiac comorbidities, including atrial fibrillation. Though this was not systematically assessed in the retrieved studies, it has been suggested as a risk factor for PAP-associated TECSA by some authors [39,40].

Another hypothesis for TECSA includes insufficient treated upper airway obstruction. For instance, Avidan showed that MAD efficacy could not be reached after several months of therapy [8] and, in response, Guilleminault and Robinson speculate that the advancement was not big enough and may lead to microarousals [41]. Similar mechanisms were found with HNS [18] and also after surgeries residual upper airway obstruction was speculated to promote TECSA [26,27]. By contrast, one study discussed a too far advancement of an MAD as a potential cause for TECSA, which might be triggered by discomfort and thus sleep instability [9]. Of note, medication that might predispose to CSA was assessed by all authors of the included studies and probably not involved in the affected patients.

Clinical management

Given the likelihood of a spontaneous resolution of TECSA, it seems reasonable to allow some time between treatment initiation and a follow-up sleep study. Our systematic review did not reveal evident subjective symptoms associated with TECSA, even though individual cases reported persistent EDS. This is quite similar to PAP-associated TECSA that may occur with typical symptoms for sleep disordered breathing but may also be asymptomatic in some patients [30]. We can thus wonder if asymptomatic patients need a specific treatment or not, especially if residual AHI and ODI are mild or moderate. Therefore, patients that report an improvement in OSA symptoms may be reassured and an objective reassessment of treatment efficacy can be performed after three to six months after treatment initiation to allow some time for the ventilatory control to adapt. Those who still complain about sleepiness should be reassessed earlier with a sleep study to differentiate between remaining residual upper-airway obstruction or TECSA. Physicians

can then also try to optimize the current treatment with interventions such as an increase or decrease in MAD protrusion, or advanced programming of an HNS including electrode configuration, stimulation amplitude, and pulse width and rate. Meanwhile, underlying comorbidities should be investigated and treated, if possible (e.g., kidney failure, heart failure, opioids). For treatments that involve surgery, it is important to wait for a healing of the surgical sites. Otherwise, swelling may not yet allow a sufficient relief of upper airway obstruction and pain as well as a still exaggerated CO_2 response may promote CSA.

Even though TECSA may resolve spontaneously, the decision to wait may be difficult in some patients. This is particularly true for those who continue to be symptomatic, those who work as professional driver, or those who present prolonged or very deep desaturations. Thus, combining the current treatment with other modalities, such as sleep position treatment, CPAP or adaptive servoventilation may be considered on an individual basis. Addition of acetazolamide or sleep stabilizing medication such as trazodone for example might be considered, but currently there are no studies to support the efficacy of these interventions in non-PAP related TECSA.

More generally, we believe that it is important to reassess systematically and objectively the efficacy of the OSA treatment to assure that those TECSA patients who might benefit from earlier interventions will not be missed. Standardized follow-up could facilitate this in clinical practice for non-PAP treatments and will also allow for a better comparison between studies and treatment modalities. In addition, body position should be considered more systematically.

Limitations

Our systematic review has several limitations. First, it is limited by the number of the retrieved studies. Second, the design of the studies was heterogeneous and given the high rate of case reports, conclusions must be drawn with caution. This also precluded us from performing a meta-analysis on prevalence, risk factors and compare treatment modalities in more detail. We tried to draw additional information from larger trials on treatment alternatives, but details on remaining respiratory events was usually too scarce, as the authors often referred to AHI only and subclassification of apnea or hypopnea types were missing. Also, after the diagnosis of TECSA, not all authors systematically searched for potential other underlying disease or treatment that could explain the CSA. We therefore could not assess thoroughly, if all cases met the definition of TECSA. Lastly, we cannot rule out that the slight increase of central events reported in the patients with TECSA might be due to night-to-night variability of CSA measurements, or to underestimation of pre-existing CSA due to different scoring methodologies, interscorer reliability or change in the sleep study signal quality.

Conclusion

Although probably rare, TECSA may occur with almost all alternative treatments for OSA management and not only with PAP-therapies. Since TECSA may be asymptomatic, follow-up studies should be performed more systematically after non-PAP initiation, within two to three months after initiation of a non-PAP device and six months after surgery. Clinicians should be aware of this rare phenomenon, its potential spontaneous resolution, but also be able to identify other pathophysiological traits such as cardiac comorbidities or medication that will need their intervention. Future studies are needed to elucidate the true prevalence, severity and clinical significance of this phenomenon.

Practice Points

1) The prevalence of TECSA is 1.8% in maxillomandibular advancement surgery and 3.3% with hypoglossal nerve stimulation according to two cohort studies.
2) Although probably rare, clinicians have to be aware that treatment-emergent central sleep apnea may also occur with alternative treatments such as mandibular advancement devices, tracheostomy or upper airway surgery.
3) A systematic reassessment of the treatment efficacy with follow-up sleep studies will help to identify TECSA, but should be scheduled in an appropriate timely manner, e.g., after three to six months after treatment initiation in asymptomatic patients as TECSA may resolve spontaneously.
4) If TECSA occurs, the underlying pathophysiology and comorbidities should be assessed in order to choose the correct intervention.

Research Agenda

Future research should:

1) Assess the true prevalence and relevance of TECSA in larger cohorts with alternative treatments to CPAP, especially with the frequently used mandibular advancement devices.
2) Determine the underlying pathophysiological mechanisms as well as patient and treatment related risk factors.
3) Determine the implication of TECSA on long-term adherence to non-PAP device treatments.
4) Assess which central apnea index threshold may be relevant and translate into cardiovascular risks.
5) Determine the consequences of TECSA on long-term outcome and residual symptoms.

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

Funding sources

None.

References

[1] Javaheri S, Smith J, Chung E. The prevalence and natural history of complex sleep apnea. J Clin Sleep Med 2009;5(3):205–11.
*[2] Nigam G, Pathak C, Riaz M. A systematic review on prevalence and risk factors associated with treatment- emergent central sleep apnea. Ann Thorac Med 2016;11(3):202–10.
[3] Westhoff M, Arzt M, Litterst P. Prevalence and treatment of central sleep apnoea emerging after initiation of continuous positive airway pressure in patients with obstructive sleep apnoea without evidence of heart failure. Sleep Breath 2012;16(1):71–8.

* The most important references are denoted by an asterisk.

[4] Pusalavidyasagar SS, Olson EJ, Gay PC, Morgenthaler TI. Treatment of complex sleep apnea syndrome: a retrospective comparative review. Sleep Med 2006;7(6):474–9.
*[5] Weitzman ED, Kahn E, Pollak CP. Quantitative analysis of sleep and sleep apnea before and after tracheostomy in patients with the hypersomnia-sleep apnea syndrome. Sleep 1980;3(3–4):407–23.
[6] Guilleminault C, Cummiskey J. Progressive improvement of apnea index and ventilatory response to CO2 after tracheostomy in obstructive sleep apnea syndrome. Am Rev Respir Dis 1982;126(1):14–20.
[7] AASM, *AMERICAN ACADEMY OF SLEEP MEDICINE (AASM)*. International classification of sleep disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
[8] Avidan AY. The development of central sleep apnea with an oral appliance. Sleep Med 2006;7(2):187–8.
[9] Gindre L, Gagnadoux F, Meslier N, Fleury B, Gustin JM, Racineux JL. Central apnea developing during treatment with a mandibular advancement device. Rev Mal Respir 2006;23(5 Pt 1):477–80.
[10] Covidence systematic review software, veritas Health innovation, melbourne, Australia. Available at: www.covidence.org.
[11] Wells G,SB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013. 30.08.2019]; http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
[12] Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. BMJ Evid Based Med 2018;23(2):60–3.
[13] Nishijima T, Sakurai S. Current therapy for central and "complex" sleep apnea syndrome. Respir Circ 2009;57(7):695–703.
*[14] Goodday RH, Fay MB. Emergence of central sleep apnea events after maxillomandibular advancement surgery for obstructive sleep apnea. J Oral Maxillofac Surg 2019;77(11):2303–7.
*[15] Patel J, Daniels K, Bogdan L, Huntley C, Boon M. Elevated central and mixed apnea index after upper airway stimulation. Otolaryngol Head Neck Surg 2020;162(5):767–72.
*[16] Mohan A, Henderson J, Jeffery Mador M. Mandibular advancement device-emergent central sleep apnea can resolve spontaneously: a case report. Journal of Clinical Sleep Medicine 2016;12(1):137–8.
[17] Kuzniar TJ, Kovacevic-Ristanovic R, Freedom T. Complex sleep apnea unmasked by the use of a mandibular advancement device. Sleep Breath 2011;15(2):249–52.
[18] Chan LC, Chang M, Aysola R, Ryden A, Mendelsohn A, Zeidler M. Central sleep apnea after hypoglossal nerve stimulation. Sleep 2018;41:A418.
[19] Sarber KM, Ishman SL, Patil RD. Emergence of Cheyne-Stokes breathing after hypoglossal nerve stimulator implant in a patient with mixed sleep apnea. JAMA Otolaryngology - Head and Neck Surgery 2019;145(4):389–90.
[20] Hong H, Oster J, Grover A, Schumaker G, Wein R, Ismail K. The emergence of cheyne-Stokes-breathing in a patient with atrial fibrillation and an implanted hypoglossal nerve stimulator. Sleep 2019;42:A421.
[21] Alshhrani WM, Kohzuka Y, Okuno K, Fleetham JA, Almeida FR. Tongue stabilizing device-emergent central sleep apnea: a case report. J Clin Sleep Med 2019;15(4):659–62.
[22] Chopra A, Das P, Ramar K, Staats B, St Louis EK. Complex sleep apnea associated with use of nasal expiratory positive airway (nEPAP) device. J Clin Sleep Med 2014;10(5):577–9.
[23] Fletcher EC. Recurrence of sleep apnea syndrome following tracheostomy. A shift from obstructive to central apnea. Chest 1989;96(1):205–9.
*[24] Corcoran S, Mysliwiec V, Niven AS, Fallah D. Development of central sleep apnea after maxillofacial surgery for obstructive sleep apnea. J Clin Sleep Med 2009;5(2):151–3.
*[25] Testani E, De Corso E, Losurdo A, Fiorita A, Vollono C, Marca GD, et al. Treatment-emergent central sleep apnoea after surgery for obstructive sleep apnoea. Acta Otorhinolaryngol Ital 2018;38(5):476–9.
[26] Goldstein C, Kuzniar TJ. The emergence of central sleep apnea after surgical relief of nasal obstruction in obstructive sleep apnea. J Clin Sleep Med 2012;8(3):321–2.
[27] Qamer SA, Samara D, Goldstein C, Stanley JJ. The emergence of central sleep apnea after surgical treatment of obstructive sleep apnea. Sleep 2015;38:A445.
[28] Sutherland K, Cistulli PA. Oral appliance therapy for obstructive sleep apnoea: state of the art. J Clin Med 2019;8(12).
[29] Ramar K, Dort LC, Katz SG, Lettieri CJ, Harrod CG, Thomas SM, et al. Clinical practice guideline for the treatment of obstructive sleep apnea and snoring with oral appliance therapy: an update for 2015. J Clin Sleep Med 2015;11(7):773–827.
*[30] Pepin JL, Woehrle H, Liu D, Shao S, Armitstead JP, Cistulli PA, et al. Adherence to positive airway therapy after switching from CPAP to ASV: a big data analysis. J Clin Sleep Med 2018;14(1):57–63.
*[31] Nigam G, Riaz M, Chang ET, Camacho M. Natural history of treatment-emergent central sleep apnea on positive airway pressure: a systematic review. Ann Thorac Med 2018;13(2):86–91.
[32] Sato K, Nakajima T. Review of systematic reviews on mandibular advancement oral appliance for obstructive sleep apnea: the importance of long-term follow-up. Jpn Dent Sci Rev 2020;56(1):32–7.
[33] Heinzer R, S. Vat, P. Marques-Vidal, H. Marti-Soler, D. Andries, N. Tobback, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med 2015;3(4):310–8.
[34] Suarez-Giron M, Bonsignore MR, Montserrat JM. New organisation for follow-up and assessment of treatment efficacy in sleep apnoea. Eur Respir Rev 2019;28(153).
[35] Hamilton RD, Winning AJ, Horner RL, Guz A. The effect of lung inflation on breathing in man during wakefulness and sleep. Respir Physiol 1988;73(2):145–54.
[36] Loewen A, Ostrowski M, Laprairie J, Atkar R, Gnitecki J, Hanly P, et al. Determinants of ventilatory instability in obstructive sleep apnea: inherent or acquired? Sleep 2009;32(10):1355–65.
[37] Salloum A, Rowley JA, Mateika JH, Chowdhuri S, Omran Q, Badr MS. Increased propensity for central apnea in patients with obstructive sleep apnea: effect of nasal continuous positive airway pressure. Am J Respir Crit Care Med 2010;181(2):189–93.
[38] Joosten SA, Landry SA, Sands SA, Terrill PI, Mann D, Andara C, et al. Dynamic loop gain increases upon adopting the supine body position during sleep in patients with obstructive sleep apnoea. Respirology 2017;22(8):1662–9.
[39] Lehman S, Antic NA, Thompson C, Catcheside PG, Mercer J, McEvoy RD. Central sleep apnea on commencement of continuous positive airway pressure in patients with a primary diagnosis of obstructive sleep apnea-hypopnea. J Clin Sleep Med 2007;3(5):462–6.
[40] Leung RS, Huber MA, Rogge T, Maimon N, Chiu KL, Bradley TD. Association between atrial fibrillation and central sleep apnea. Sleep 2005;28(12):1543–6.
[41] Guilleminault C, Robinson A. Central sleep apnea, upper airway resistance and sleep - Response. Sleep Med 2006;7(2):189–91.