Chapter 25
The Positioning Approach is Not Only a Marketing Strategy

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Introduction

Since the beginning of CPAP (continuous positive airway pressure) use in the 1980s, by Dr. Colin Sullivan [1], until the mid-2000s, sleep-disordered breathing treatment primarily focused on obstructive sleep apnea (OSA). Central respiratory events, including complex apnea (known today as treatment-emergent central apnea) were targeted for servo-ventilator treatment. Little was known about the sleep physiology and pathophysiology. Phenotypic characteristics and overlap with other pathologies were timidly explored. Mixed apneas were treated as obstructive events since knowledge and access to respiratory flow curves during sleep were basically limited to clinical research (algorithms of the positive pressure devices were difficult to access, their limitations for the interpretation of respiratory events during sleep were not known) [2]. Over the years, studies onto respiratory disturbances during sleep have deepened. The precision medicine concept in sleep area has begun and nowadays; it is necessary to have a broad knowledge of both pathophysiological processes and individual characteristics for effective and assertive treatment of respiratory disorders by using positive pressure.

Treatment-emergent central sleep apnea (TECSA) is characterized by the appearance of central sleep apnea/hypopnea (CSA) while undergoing treatment for OSA was initially observed in some patients who primarily had OSA after the significant resolution of the obstructive events by treatment with a positive airway pressure (PAP) device. Although it is more commonly reported during the initiation of PAP

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therapy, it is currently known that the TECSA could occur after various treatment modalities for OSA, including the use of a mandibular advancement device (MAD), maxillomandibular advancement surgery, sinus or nasal surgery, and also myofunctional therapy [3, 4]. The prevalence of TECSA vary widely among different studies ranging from 0.56 to 20.3% and it is considered a non-hypercapnia-induced central sleep-disordered breathing [3, 5].

Potential pathophysiological mechanisms for TECSA include low arousal threshold, ventilatory control instability (expressed by high loop gain in patients with OSA and the presence of upper airway narrowing during central apneas and hypopneas), prolonged circulation time, and activation of lung stretch receptors [3, 6, 7]. The central respiratory events seen in TECSA may be transient and resolve spontaneously through strict adherence to the assigned therapy, but in some patients, they persist even with regular therapy maintenance [3, 5].

There is controversy about the optimal method for treating TECSA. With regard to PAP treatment, studies have shown that CSA events naturally disappear after few months with the maintenance of CPAP. Bilevel PAP (Bilevel) with or without a back-up respiratory rate can be an effective alternative for treating TECSA in patients who do not respond to CPAP. And Adaptive Servo-Ventilation (ASV) could be a treatment option for patients whose TECSA does not improve after use of CPAP or Bilevel. Medications could be selected to improve ventilatory control stability or elevate the arousal threshold for TECSA patients, which may be a supplement to PAP therapy, but there are no large sample clinical trials to confirm the effectiveness and safety of such therapeutic options. More evidence is needed before recommending oxygen therapy or carbon dioxide (CO_2) supplementation as viable treatments options for TECSA [3, 7, 8].

Specifically in relation to pressure therapy, the development of TECSA may affect the effectiveness of OSA treatment and patient compliance [3]. Inadequate ventilation strategies can, in turn, trigger central respiratory events, if the emergence of these events is associated with ventilatory control instability or a high arousal threshold. Thus, it is extremely necessary to identify TECSA, as well as to conduct a detailed analysis of the facts for an adequate resolution of the problem.

Patient Information

A.C.G., a 59-year-old man, was referred to the PAP therapy adaptation program, complaining of non-restful sleep, nightmares, snoring, and hypersomnia. Diagnostic polysomnography (PSG) presented an apnea-hypopnea index (AHI) of 32.0 respiratory events/hour and titration study suggested a CPAP pressure of 13 cmH_2O. The patient started pressure therapy with an Auto-PAP at 5.6–13 cmH_2O. During a follow-up visit at 2 weeks with an average of hours of CPAP use of 5:14 h and residual AHI of 3.3/h, the patient still complained of non-restorative sleep and daytime sleepiness. At the respiratory flow curve analysis, we observed central sleep apneas typical of TECSA events.

Diagnostic Assessment

Basal Polysomnographic Examination

The total recording time was 494.9 min. Stage N1 latency was 9.5 min (normal <30 min), and rapid eye movement (REM) sleep latency (REMSL) was 137.0 min (normal = 70–120 min). The total sleep time (TST) was 389.5 min (78.7% sleep efficiency (SE); normal >85%) and the percentages of sleep stages in relation to TST were N1: 12.3%; N2: 49.0%; N3: 18.2% REM sleep: 20.4%. Wake time after sleep onset (WASO) was 95.9 min. 223 registered micro-awakenings (duration <15 s), with an index of 34.4/h (normal <10/h). Two-hundred eight breathing pauses were recorded during sleep, divided into 62 apneas (4 obstructive, 38 mixed, 20 central) and 146 hypopneas. These breaks lasted between 10.0 and 59.0 s (average duration = 18.0 s), with an average oxygen saturation (SaO_2) of 95% and a minimum of 85%. The SaO_2 remained below 90% during 0.4% of total sleep time. The index of apnea-hypopnea was 32.0/h (normal <5/h). Moderate-to-high snoring intensity was recorded. Mean heart rate was 55.2 bpm (sinus rhythm). There were 69 periodic movements of the lower limbs, with 2 events associated with awakening. The index of periodic limb movements (PLMi) was 10.6/h (normal <15/h). The sleep laboratory evaluation showed: (1) Marked increase in AHI (32.0/h), with respiratory pauses associated with oxyhemoglobin desaturation (minimum SaO_2 of 85%) and/or micro-awakenings; (2) Constant, moderate-high intensity snoring on the night of assessment; (3) Normal movement index (10.6/h); (4) Sleep architecture with: (a) reduced SE (78.7%), (b) increased WASO (95.9 min), (c) normal NREM sleep latency (9.5 min), (d) increased REMSL (137.0 min), (e) percentage of N3 normal (18.2%), (f) increased N1 percentage (12.3%), (g) percentage of normal REM sleep stage (20.4%); (5) Increased micro-awakening rate (34.4/h).

Polysomnography for CPAP Titration

A new PSG was conducted to regulate CPAP pressute. The total registration time was 401.2 min. Stage N1 latency was 4.5 min (normal <30 min), and REM sleep was 55.0 min (normal = 70–120 min). The TST was 329.5 min (82.1% efficiency; normal >85%) and the percentages of sleep stages in relation to total sleep time were N1: 4.1%; N2: 49.0%; N3: 26.4%; REM sleep: 20.5%. The WASO was 67.2 min. One-hundred sixty-three micro-awakenings were recorded (duration <15 s), with an index of 24.9/h (normal <10/h). A nasal mask (size XL) (Fig. 25.1a) was used until 2:25h when it was changed to another model of nasal mask from other brand (size L) (Fig. 25.1b), with manual pressure adjustment. With CPAP pressure set at 13 cmH_2O, the patient did not snore, and no significant oxyhemoglobin desaturation was observed (minimum SaO_2 = 88%). In the total night (assessment of all pressure levels), 66 respiratory pauses were recorded during sleep, divided into 17

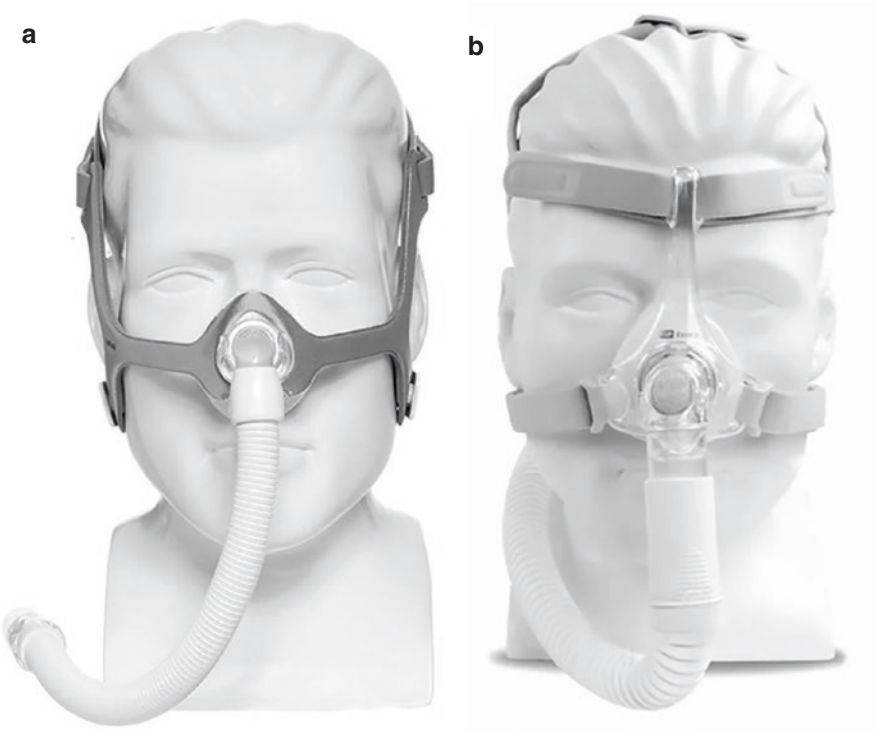

Fig. 25.1 (**a**, **b**) Different nasal route masks from different brands. The main difference between these two models of nasal masks is the forehead support. Original figure. Image courtesy of Dr. Vivien Schmeling Piccin

apneas (2 obstructive, 0 mixed, 15 central) and 49 hypopneas. These pauses lasted between 10.0 and 26.5 s (average duration = 18.1 s), with mean SaO_2 of 94% and minimum of 88%. SaO_2 remained below 90% during 0.3% of TST. The AHI was 12.0/h (normal <5/h). Mean heart rate was 54.8 bpm (sinus rhythm). There were observed 116 periodic lower limbs movements, with 20 events associated with awakening. The total rate of periodic was 17.7/h (normal <15/h). The evaluation showed: (1) Considering, in each therapeutic adjustment evaluated, the sleep time, the presence of REM sleep and supine position, better control of breathing events occurred with CPAP at a pressure of 13 cmH_2O; (2) With CPAP at a pressure of 13 cmH_2O: normal AHI (4/h), associated with no relevant oxyhemoglobin desaturation and/or micro-arousals (snoring abolished); (3) Slight increase in PLMi (17.7/h); (4) Increased micro-awakening rate (24.9/h).

Computed Tomography of the Face and Paranasal Sinuses

The face computed tomography (CT), prescribed by the otorhinolaryngologist, was performed without contrast (Fig. 25.2) and revealed nasal septum inclined to the left in the anterior cartilaginous portion and deviated to the right in the other portions, with a bone spur to the left that remodels the inferior nasal turbinate on this side.

- Asymmetrical ethmoid fovea, lower on the right
- Pneumatization of the vertical lamella of the right middle concha
- Bilateral wide ethmoid bulla
- Prominence of the mucous component of the turbinates and nasal cavities
- Slight thickening of the mucous lining of all paranasal cavities, with probable small retention cyst/polyp in the left maxillary sinus
- Discreet amount of secretion with bullae in right posterior ethmoid cell
- There is no liquid level
- Infundibulum, frontal and sphenoethmoidal recesses patent
- Rhinopharynx of regular contours
- Elongated soft palate
- Tongue with increased dimensions and verticalization of its longitudinal axis
- Topical hyoid bone
- And prominent palatine and lingual tonsils, with reduced pharyngeal air column caliber (these findings can be found in individuals who snore or have OSA).

Additional findings: Hypoattenuating material fills some mastoid cells and coats the right tympanic cavity. The anteroposterior diameter of the left eyeball is increased.

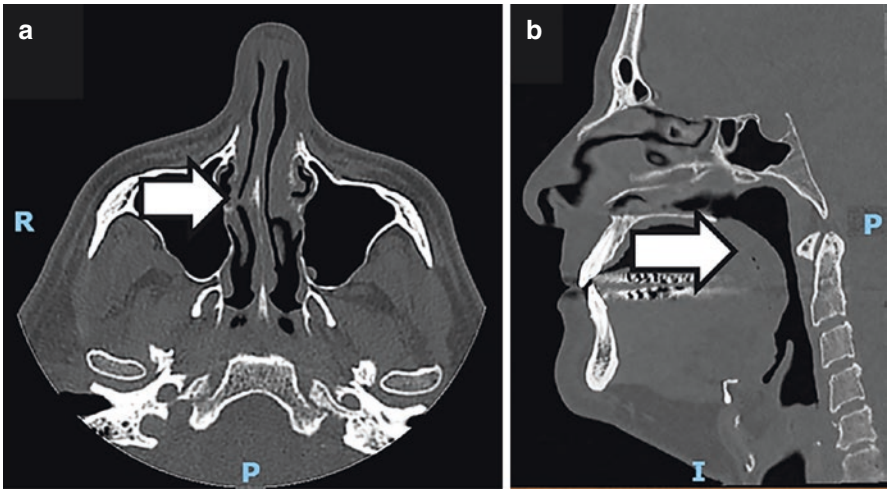

Fig. 25.2 Computed tomography of sinuses and face showing (white arrows): (**a**) Nasal septum inclined to the left in the anterior cartilaginous portion and deviated to the right in the other portions and (**b**) Elongated soft palate with reduced pharyngeal air column caliber. *R* right, *P* posterior, *I* inferior. Reprinted with permission from A.C.G

Clinical Findings

The patient reported that he usually goes to sleep at 22:00 and wakes up at 5:30. He reported fragmented sleep, snoring, nightmares, and daytime sleepiness. He also reported previous hernia treatment in the lumbar spine and pituitary adenoma. The patient was in treatment with pantoprazole, rosuvastatin and cabergoline. Previously underwent surgery to lumbar hernia correction and arthroscopy in the right knee. He reported moderate alcohol consumption (4 times a week) and moderate physical activity. He never smoked. The physical examination presented weight of 94 kg, height of 178 cm, BMI of 29.7 kg/m^2, modified Mallampatti score III, SaO_2 of 97%, HR of 65 bpm, and Epworth scale of 10.

Timeline

The timeline show the historical and current information of this case report is depicted in Fig. 25.3.

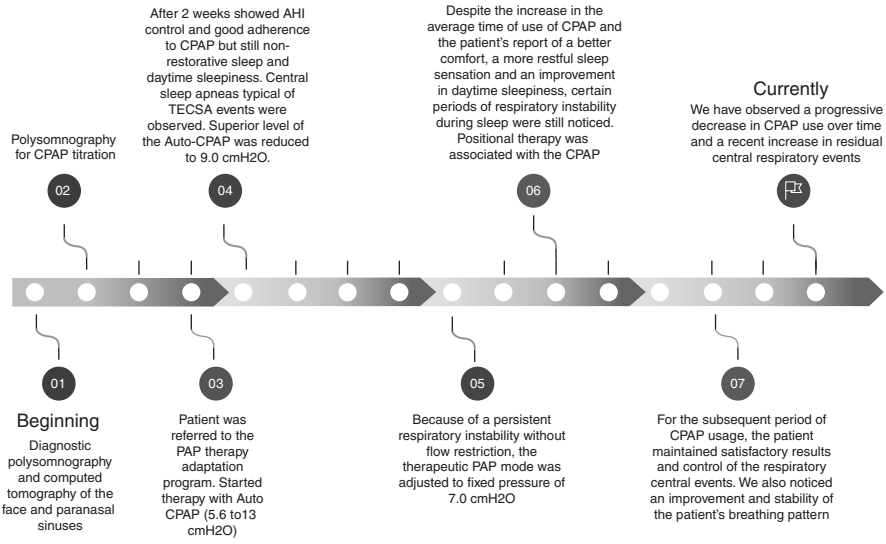

Fig. 25.3 Timeline panel showing the historical and current information from this case report. *CPAP* continuous positive airway pressure, *PAP* positive airway pressure, *AHI* apnea hypopnea index, *TECSA* treatment-emergent central sleep apnea

Physiotherapeutic Intervention

As previously described, the patient started pressure therapy with an Auto-PAP between 5.6 and 13 cmH_2O. In a follow-up visit after 2 weeks, he still complained of non-restorative sleep and the same daytime sleepiness. Moreover, at respiratory flow curve analysis, we observed central sleep apneas typical of TECSA events (Fig. 25.4).

Considering the respiratory instability observed at the beginning of the Auto-CPAP treatment, the superior level of the Auto-CPAP was reduced to 9.0 cmH_2O. We observed a persistent respiratory instability, but without inspiratory flow restriction. On the other hand, we observed a slight increase in the number of residual central respiratory events and patient reported still a little daytime sleepiness. So, aiming a breathing pattern improvement and patient comfort, and considering the existence of a probable instability of the respiratory center (increased by excessive pressure support), the therapeutic mode was adjusted to a fixed pressure of 7.0 cmH_2O.

Despite patient comfort and improvement in sleepiness symptoms, respiratory instability during sleep was still noticed (distributed at specific night periods). We raised the hypothesis of the upper airway collapse related to sleep positioning (due to palatal prolapse, because CT showed an elongated soft palate). Moreover, we

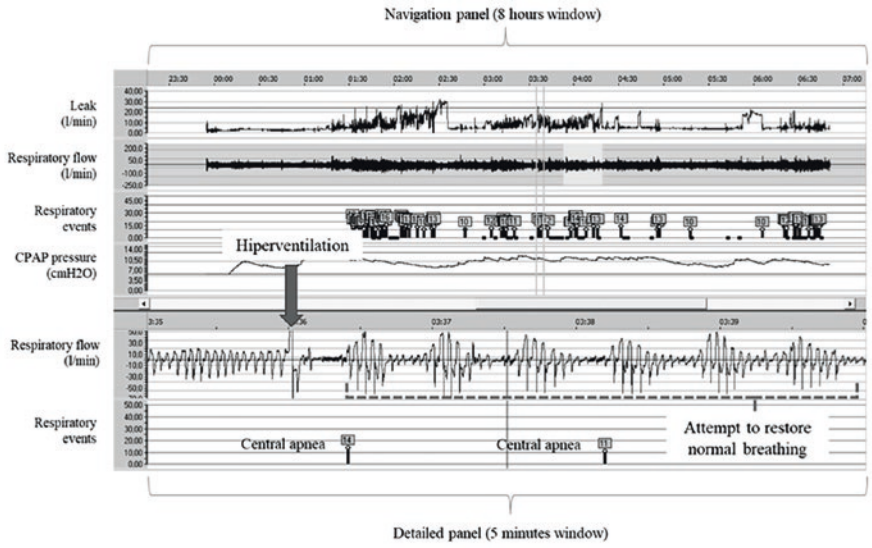

Fig. 25.4 Screen of a graphical data presentation, extracted from positive pressure equipment. The arrow shows a physiological sigh event, with a considerable increase in respiratory flow (hyperventilation). Next, we observe that the inspiratory flow curve diminishes, in response to the carbon dioxide level decrease caused by the increase in respiratory amplitude, as observed in the previous respiratory cycle. In a 5-min window, we observed the maintenance of a subsequent respiratory instability, including two central apnea events triggering detected by the equipment algorithm. Reprinted with permission from A.C.G

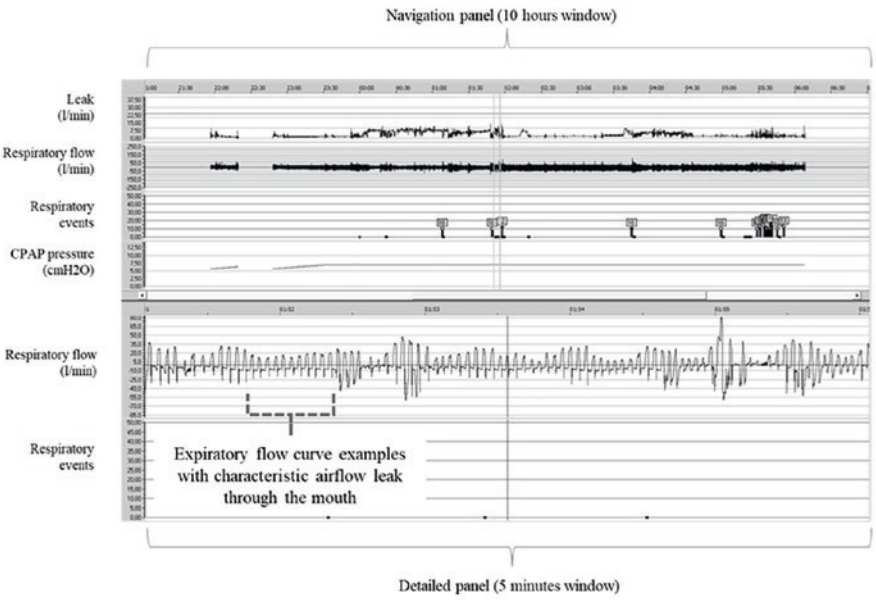

Fig. 25.5 Oral leakage can also occur due to prolapse of the soft palate during expiration, causing obstruction of the nasopharynx and air leakage through the mouth. This specific type of mouth leak can be detected by analyzing the airflow shape obtained on CPAP data card. Reprinted with permission from A.C.G

found a characteristic expiratory flow curve at the CPAP data (Fig. 25.5), corroborating the hypothesis of palatal prolapse [9, 10]. These data added to the hypothesis of high loop gain presented by the patient could be the factors responsible for the ventilatory disorder, resulting in the emergent central apneas. In fact, the product of "control gain—CG" (represented by the sensitivity of central and peripheral chemoreceptors) versus "plain gain—PG" (represented by the effectiveness of the lungs to alter blood gases, plus the increase in factors that lead to collapse of the UA), determines the magnitude of the LG. There might be a dynamic LG increase with the adoption of the supine position during sleep [11]. In our case, we considered that adding a positional device could infer to the decrease respiratory response magnitude to a probable palatal prolapse (maybe, due to a supine position). As an adjunct to the PAP treatment, a positional therapy was introduced with a positioning vest, maintaining the therapeutic pressure fixed at 7.0 cmH_2O.

Follow-Up and Outcomes

Without pressure adjustments, just adding the positional therapy along CPAP use, a good therapeutic result was observed and for the subsequent period of CPAP usage, the patient maintained satisfactory results and control of the respiratory central

events (Table 25.1). We also observed an improvement and stability of the patient's breathing pattern, as seen in Fig. 25.6.

During the patient follow-up, we performed a small increment in the therapeutic pressure, to correct inspiratory flow curve limitation during sleep. Unfortunately, we have observed a progressive decrease in CPAP use over time and a recent increase in residual central respiratory events (Table 25.1).

Table 25.1 Main results of the initial period of CPAP usage and subsequent follow-up

	Two-week period of initial CPAP use	Subsequent period of CPAP use	Subsequent period of CPAP use	Subsequent period of CPAP use	Subsequent period of CPAP use
Usage days/total days (percentile of more than 4 h of usage per night)	15/15 (100%)	2/2 (100%)	7/77 (84%)	142/386 (60%)	176/300 (54%)
Mask	Nasal	Nasal	Nasal	Nasal	Nasal
Pressure (cmH_2O)	5.6–13.0	5.6–9.0	7.0	7.0	7.2
95th percentile pressure (cmH_2O)	11.2	8.9	7.0	7.0	7.2
Median pressure—cmH_2O	9.4	8.0	7.0	7.0	7.2
Average usage (total days) (h)	6:46	6:50	7:13	4:00	3:34
Median usage (days used) (h)	6:42	6:50	6:11	6:30	6:11
Expiratory relief	Off	Off	Off	Off	Off
95th percentile leaks (L/min)	13.2	14.4	6.6	6.0	7.5
Median leaks (L/min)	3.6	4.2	2.4	0.0	0.6
Events per hour (residual AHI)	8.5	8.8	9.4	4.8	6.3
Central apnea index	4.0	4.4	3.7	1.4	3.1
Obstructive apnea index	0.6	0.6	0.8	0.3	0.4
Obstructive hypopnea index	3.8	3.8	4.8	3.0	2.7
Unknown apnea index	0.0	0.0	0.0	0.0	0.0

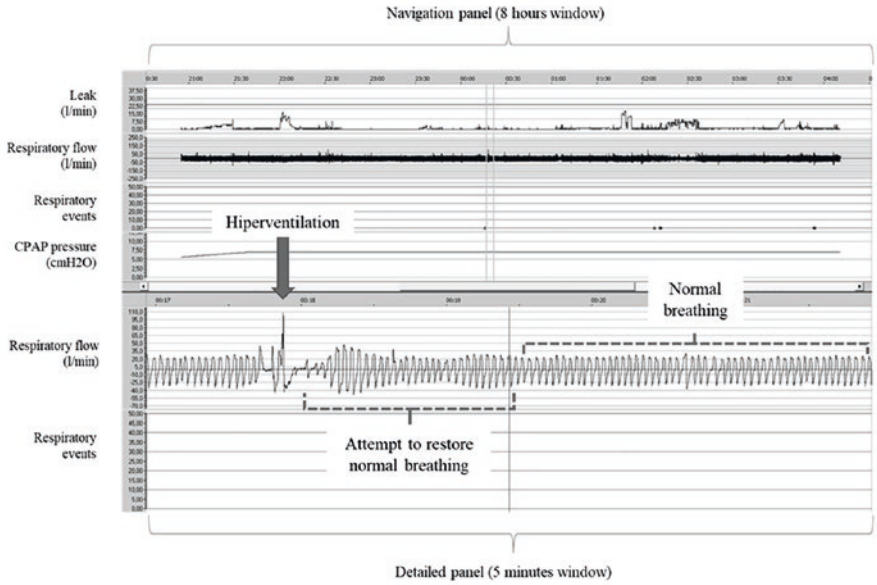

Fig. 25.6 Screen of a graphical data presentation, extracted from positive pressure equipment. The arrow shows a physiological sigh event, with a considerable increase in respiratory flow (hyperventilation). Next, we observe that the inspiratory flow curve diminishes, in response to the carbon dioxide level decrease caused by the increase in respiratory amplitude, as observed in the previous respiratory cycle. In a 5-min window, we observed a faster recover of the normal respiratory flow curve, in relation of what was observed at initial period of CPAP use, as showed before in Fig. 25.4. Reprinted with permission from A.C.G

Discussion

It is important to observe that central apnea rarely occurs as a single event; instead, it occurs in cycles of apneas or hypopneas, alternating with hyperpnea, a reflection of the negative feedback closed-loop cycle that characterizes ventilatory control (often described by using the concept of "loop gain") [6]. In our case report, it seems that TECSA was a loop gain event mainly caused by two factors: (a) chemoreflex sensitivity (controller gain) reflecting the response of the ventilatory system to changing pressure of end tidal carbon dioxide (the controller); and (b) the upper airway anatomy causing the inspiratory flow restriction on the supine position by palatal prolapse [11, 12].

TESCA treatment remains a gray area, and caution is recommended when a therapeutic approach is extrapolated from other forms of central apnea. Increased pressure or Auto-CPAP for patients with respiratory instability may not be a good therapeutic alternative [13], as it may trigger more central respiratory events, the association of positional therapy to control palatal prolapse, and, consequently, maintain upper airway permeability during sleep seems reasonable. In fact, the literature shows that in 61.5% of patients with primary CSA, positioning during

sleep is the main causal factor of central respiratory events [14] and the positional therapy could improve CSA optimizing the treatment of associated comorbid conditions [15].

In this case report, positional therapy associated with CPAP improved TECSA, but still with residual CSA events. The literature shows that about a third of patients with TECSA may continue to exhibit persistence of CSA on reevaluation, and the pathophysiological mechanisms for that remain unknown [3, 5]. But, in our case, one plausible explanation for the residual central apneas observed could be that the CO_2 reservoir and the apnea threshold for the patient are labile as a direct consequence of the intermittent PAP usage and CPAP use decrease over time (as presented on Table 25.1). This view is supported by experiments that have demonstrated that the magnitude of reduction in $PaCO_2$ below eupneic $PaCO_2$ and the transient increase in alveolar ventilation required to attain the apneic threshold is not a constant value. This variability in the apneic threshold by the non-regular CPAP use could lead to persistence of central apneas on PAP therapy depending on the degree of patient adaptation of chemoreceptors to the fluctuating CO_2 reservoir and the apneic threshold [5]. Another justification for central respiratory events is that, over time, the patient no longer uses positional therapy associated with CPAP.

In fact CPAP compliance is still a challenge and has been reported to range from 40 to 84% [16]. Adherence to long-term positional therapy was hampered by patient-reported discomfort, and the reliability of adherence information is also hampered by the subjective assessment of the data. One study evaluated tennis ball technique and found that long-term adherence was less than 10%. Another group studied patients wearing a supine sleeping position preventive vest and found adherence lower than 30%, in an average period of 24 months of use of positional therapy [17].

In our case, the patient reported that traveled often for work and the equipment size was an impediment to take it on his travels. He was currently considering the possibility of purchasing a mini-CPAP to make it easier to carry on when traveling. The patient also reported that he is no longer using positional therapy .

Take-Away Messages

1. TECSA is a complex process that can combine central respiratory instability as well as unfavorable upper airway structure and function.
2. It requires a careful assessment of the patient, including, in addition to polysomnographic examinations, information of the upper airway anatomy.
3. Treatment includes identifying the underlying causes and treating any precipitating factors.
4. The use of combined therapies can be a simple and cost-effective solution for treatment-emerging central apnea management.
5. Therapy compliance is still a challenge.

Patient Perspective

"Around 2015, I started to suffer with tiredness and drowsiness during the day. My endocrinologist, in mid-2019, referred me to a sleep doctor. It was found that there were several apneas during my night's sleep, and this was the cause of my daily discomfort. I was then referred to a sleep physiotherapist to start the CPAP therapy. With the frequent use of the equipment, I have had very regular periods of sleep, with a much lower number of respiratory events that occurred in the period when I did not use the device. The consequence of this continuous CPAP use is that I no longer suffer from tiredness and drowsiness during the day."

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