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CASE REPORTS

The level of carbon dioxide is the determinant of successful noninvasive ventilation pressure titration in patients with nonhypercapnic primary central sleep apnea: a case report

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Primary central sleep apnea is classified as nonhypercapnic central sleep apnea. High loop gain, lower CO_2 reserves, and other reasons can lead to hypocapnia in patients who develop intermittent hyperventilation during sleep. Therefore, it is necessary to monitor nocturnal CO_2 level for these patients. We report a female patient diagnosed with nonhypercapnic primary central sleep apnea who complained of snoring, apnea, and excessive daytime sleepiness. With the monitoring of transcutaneous partial pressure of CO_2, manual noninvasive ventilation pressure titration was performed with continuous positive airway pressure, bilevel positive airway pressure in a spontaneous-timed mode, and adaptive servo-ventilation mode for 3 nights, respectively. Only adaptive servo-ventilation mode could stabilize the transcutaneous partial pressure of CO_2 above the apneic threshold (approximately 40 mm Hg) with successfully eliminating central apnea events. It is concluded that the level of CO_2 is the determinant of successful noninvasive ventilation pressure titration in patients with nonhypercapnic central sleep apnea.

Keywords: non-hypercapnic, central sleep apnea, transcutaneous partial pressure of carbon dioxide, loop gain, apneic threshold, adaptive servo-ventilation
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INTRODUCTION

The *International Classification of Sleep Disorders*, third edition, classifies the central sleep apnea syndromes into 8 types. Among them, primary central sleep apnea (CSA), CSA with Cheyne-Stokes breathing, CSA due to high-altitude periodic breathing, and treatment-emergent CSA are belonged to nonhypercapnic CSA, also called hypocapnic CSA.[1] The primary CSA is also referred to as "idiopathic CSA" in the absence of an identifiable etiology. Perhaps posthyperventilated hypocapnia is the underlying pathophysiological mechanism of primary CSA. Intermittent hyperventilation is associated with increased chemoreceptor sensitivity and sleep instability. CSA will ensue if the arterial partial pressure of carbon dioxide ($PaCO_2$) falls below an individual's specific value (apneic threshold [AT]).[2,3] We report a case diagnosed with primary CSA, in which manual noninvasive ventilation pressure titration was performed for 3 nights with continuous positive airway pressure (CPAP), bilevel positive airway pressure in a spontaneous-timed mode (BPAP-ST), and adaptive servo-ventilation (ASV) modes, respectively, polysomnography, and transcutaneous partial pressure of CO_2 ($PtcCO_2$) monitored simultaneously. Only the ASV mode could maintain $PtcCO_2$ at a stable level of 40–44 mm Hg and successfully eliminate central apnea events, while both CPAP and BPAP-ST failed.

REPORT OF CASE

A 75-year-old female with hypertension, coronary heart disease, and cardiac function level II (New York Heart Association) complained of snoring, sleep apnea, and excessive daytime sleepiness for more than 10 years and she her Epworth Sleepiness Scale score was 15/24. In addition, the patient manifested poor mental status, memory loss, dry mouth, and frequent urination during sleep. Physical examination showed body mass index of 26.7 kg/m^2, neck circumference of 35 cm, waistline of 109 cm, and mild stenosis of a pharyngeal cavity (Friedman grade I). The blood cell analysis revealed B-type natriuretic peptide increased to 236 pg/ml. Blood gas analysis showed PH of 7.44, $PaCO_2$ of 34 mm Hg, PaO_2 of 80 mm Hg, HCO_3^- of 23.1 mmol/L, and pulmonary function was normal. Cardiac color Doppler ultrasound revealed that the left ventricular ejection fraction was 63%, and the pulmonary artery systolic pressure was 25 mm Hg. No obvious abnormal images were found in the chest and head enhanced computerized tomography. Nocturnal in-laboratory polysomnography (Philips Alice 6, Murrysville, USA) and $PtcCO_2$ (Radiometer TCM4, Copenhagen, Denmark) demonstrated lots of central apnea events with the average $PtcCO_2$ of 39 mm Hg, the highest $PtcCO_2$ of 43 mm Hg (**Table 1**, **Figure 1A**). Neither Cheyne-Stokes breathing nor periodic breathing pattern was seen in polysomnography. According to the daytime $PaCO_2$ (34 mm Hg) and the nocturnal $PtcCO_2$ (37–43 mm Hg) in *International*

Table 1—The results of PSG diagnosis and NIV titration.

Indicator	Diagnosis	Titration 1	Titration 2	Titration 3	Follow-up
Mode	PSG	CPAP	BPAP-ST	ASV1	ASV2
AHI, events/h	52.8	30.0	57.5	2.2	4.3
CAI, events/h	26.7	22.5	33.8	0	0.3
ArI, times/h	31.2	24.2	38.8	13.3	12.9
ODI, events/h	49.2	30.5	41.4	4.3	5.4
Min SpO_2, %	82	87	89	91	91
Mean SpO_2, %	93	93	95	96	98
T90(%)	6.7	1.3	0.3	0	0
N1, %	36.4	25.0	62.0	20.9	20.3
N2, %	47.6	60.0	38.0	48.1	53.8
N3, %	8.6	4.3	0	14.9	12.6
REM, %	7.3	10.7	0	16.1	13.3
$PtcCO_2$, mmHg	37–43	38–40	37–39	40–42	41–44
ESS	15	15	15	6	3

AHI = apnea-hypopnea index, ArI = arousal index, ASV = adaptive servo-ventilation, BPAP-ST = bilevel positive airway pressure in a spontaneous-timed mode, CAI = central apnea index, CPAP = continuous positive airway pressure, ESS = Epworth Sleepiness Scale, NIV = noninvasive ventilation, ODI = oxygen desaturation index, PSG = polysomnography, $PtcCO_2$ = transcutaneous monitoring of carbon dioxide, REM = rapid eye movement, SpO_2 = pulse oxygen saturation, T90(%) = percentage of time with oxygen saturation less than 90%.

Classification of Sleep Disorder, third edition, the patient was diagnosed with nonhypercapnic primary CSA.

Then manual NIV titration (Weinmann PrismaLAB, Hamburg, Germany) was initiated in our sleep center. On the first night, CPAP mode was applied to the patient. When the pressure rose to 8 cm H_2O in nonrapid eye movement or 10 cm H_2O in rapid eye movement, the obstructive respiratory events disappeared. A total of 173 events of central apnea existed, and the $PtcCO_2$ was maintained at 38–40 mm Hg (**Table 1**, **Figure 1B**). The next day, the patient underwent the second night titration with BPAP-ST mode. The pressure increased to 12/8 cm H_2O (backup frequency: 14 times/min), lots of central apnea events and frequent desaturation emerged, and the $PtcCO_2$ was maintained at 37–39 mm Hg (**Table 1**, **Figure 1C**). On the third night, we changed to ASV mode (EEPAP min: 5 hPa, EEPAP max: 13 hPa, PDIFF norm: 5 hPa, PDIFF max: 10 hPa, auto frequency F: open). The central apnea events disappeared and sleep quality of the patient clearly improved. The $PtcCO_2$ was maintained at 40–42 mmHg (**Table 1**, **Figure 1D**). Subsequently, the patient felt that the symptoms are significantly relieved, with a decreasing Epworth Sleepiness Scale score of 6/24. One week later, the patient was followed up for the second overnight titration with ASV mode (EEPAP min: 7 hPa, EEPAP max: 10 hPa, PDIFF norm: 4 hPa, PDIFF max: 8 hPa, auto F: open). The polysomnography results demonstrated the obstructive and central respiratory events almost disappeared, and the $PtcCO_2$ was maintained at 41–44 mm Hg steadily. The patient kept in the supine position all the time during 4 nights.

In this case, we noticed that lots of central apnea events emerged when the $PtcCO_2$ dropped below 40 mm Hg in either CPAP or BPAP-ST mode. The BPAP-ST further reduced $PtcCO_2$, which aggravated CSA. ASV could maintain stable breathing by keeping the $PtcCO_2$ above 40 mm Hg, and CSA and hypoxia were well controlled.

DISCUSSION

Primary CSA is virtually a diagnosis of exclusion after excluding the known causes of CSA. So far, the etiology and underlying mechanisms are still unclear. These patients tend to have an increased ventilatory response to CO_2. CSA mostly results from withdrawal of the wakefulness drive in sleep leaving ventilation under metabolic control.[4] As we know, the ventilation stability is controlled by a chemical and mechanical system through a negative feedback mechanism during sleep. The nonrapid eye movement sleep period is characterized by a sharp reduction in motor output of the upper airway and respiratory pump muscles, which results in a mild to moderate sustained hypoventilation in healthy people, and ultimately leads to an increase in $PaCO_2$ of 2–8 mm Hg.[5] Patients with primary CSA manifest an elevated chemoreceptor sensitivity to the changes of $PaCO_2$ (high controller gain),[6] along with ventilation instability and sleep state instability. Thus, slight changes in $PaCO_2$ will cause strong ventilatory response. Because of delayed feedback time, this process cannot be fed back in a timely way to

Figure 1—Polysomnography results.

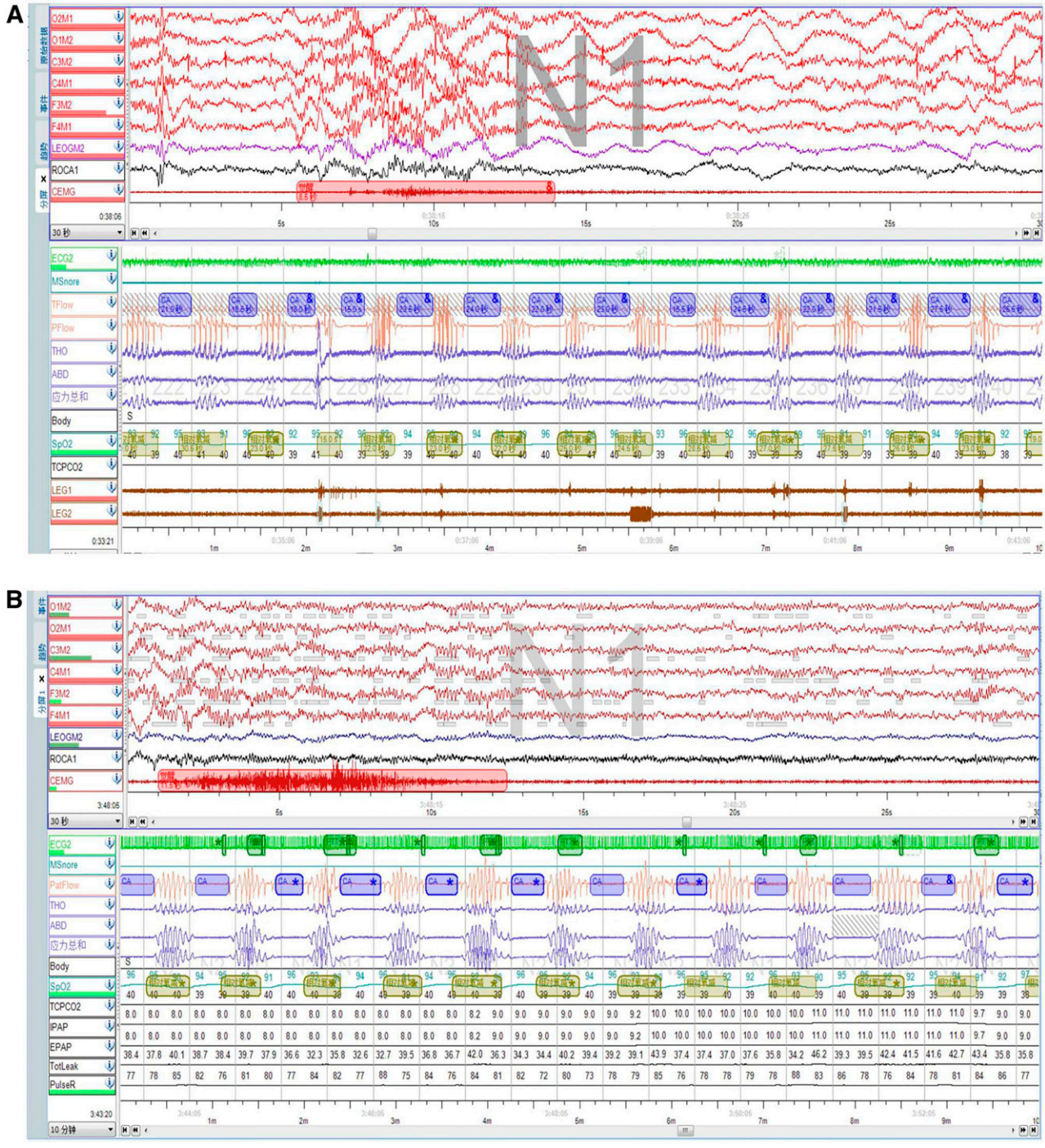

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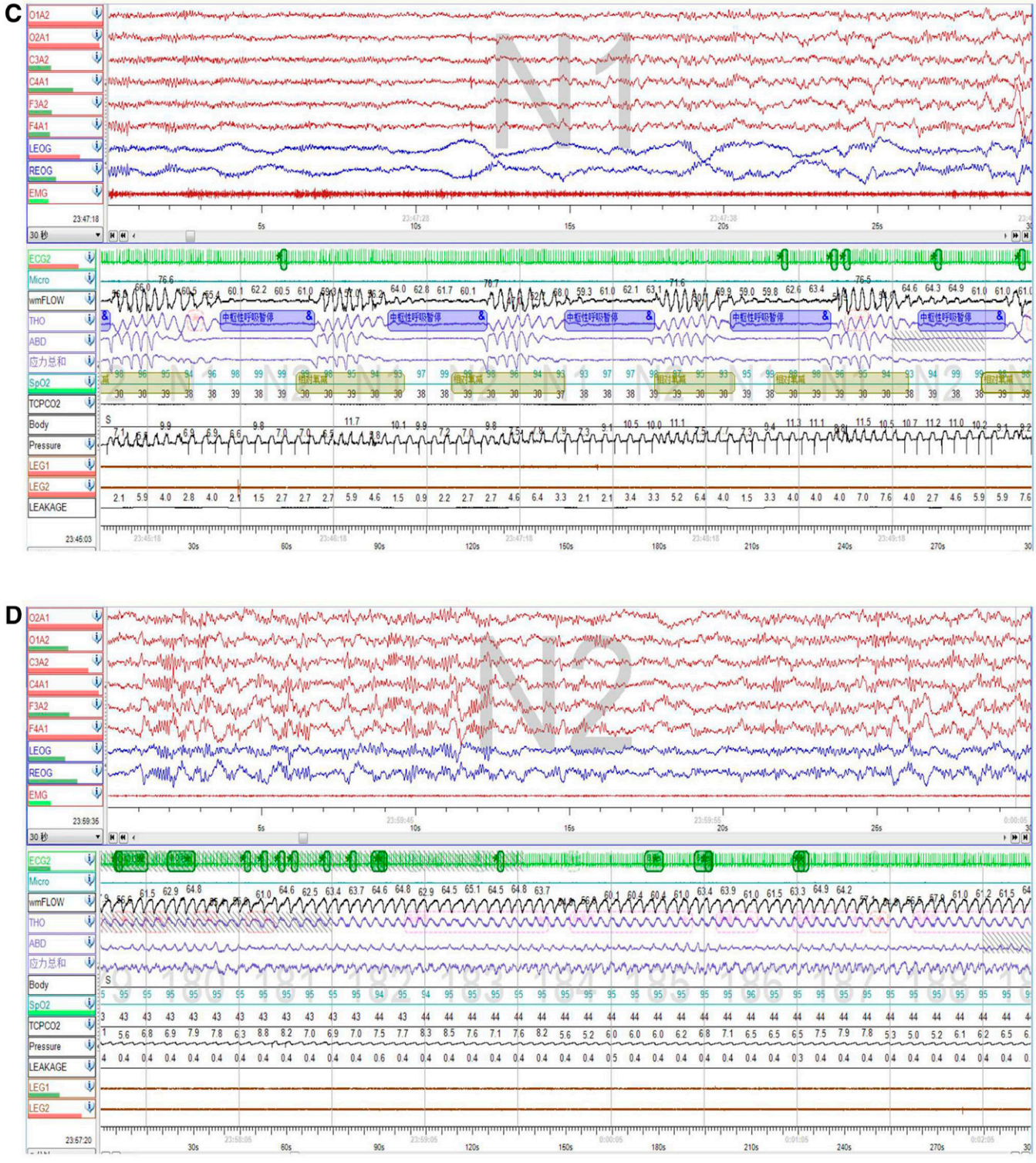
Figure 1—Polysomnography results. (*Continued*)



(A) Baseline polysomnography (PSG) showing many central apnea events and desaturation without Cheyne-Stokes breathing (CSB). Transcutaneous partial pressure of carbon dioxide ($PtcCO_2$) between 37 and 43 mm Hg. **(B)** Many central apnea events and desaturation during the course of continuous positive airway pressure mode pressure titration. $PtcCO_2$ between 38 and 40 mm Hg. **(C)** Many central apnea events and desaturation during bilevel positive airway pressure mode pressure titration. $PtcCO_2$ between 37 and 39 mm Hg. **(D)** During the course of adaptive servo-ventilation mode pressure titration, central apnea events and desaturation disappeared. $PtcCO_2$ between 40 and 42 mm Hg. LEOG, light electro-oculographic; REOG, right electro-oculographic; CEMG, submental (chin) electromyographic; ECG, electrocardiograph; MSnore, micro snoring; TFlow, thermal flow; PFlow, pressure flow; THO, thorax effort; ABD, abdomen effort; Body, body position; LEG, leg electromyographic.

the respiratory center and hyperventilation continues for several respiratory cycles and then results in hypocapnia, which will cause CSA when the CO_2 level drops below the AT.[2,5,7] In other words, CSA will ensue if the $PaCO_2$ falls below the AT, and ventilation will not resume until $PaCO_2$ rises subsequently above the recruitment threshold. The important factor that determines the propensity to develop CSA is the difference between $PaCO_2$ during eupnea and the AT, namely CO_2 reserve.[3,5] The smaller the CO_2 reserve, the more likely CSA will occur.[8] In this case, we noted that central respiratory events and desaturation emerged so long as $PtcCO_2$ was below 40 mm Hg during NIV titration. Thus, we speculated the AT of this patient was about 40 mm Hg in $PaCO_2$.

NIV therapy is effective in improving respiratory stability. The updated practice parameters published by the American Academy of Sleep Medicine recommend that NIV therapy can be considered for patients with primary CSA.[1] CPAP should be applied as a first-line treatment with or without oxygen. However, if CSA is not resolved on CPAP and/or oxygen, ASV should be considered.

In our case, neither CPAP nor BPAP-ST was effective in the treatment of primary CSA. BPAP-ST provided a pressure support and a backup rate. In theory, central apneas should not happen when a backup rate was present. However, it was worth noting that there were still many central apnea events either with CPAP or BPAP-ST, because the $PtcCO_2$ fell below AT (approximately 40 mm Hg) in these 2 modes. In particular, we found that the patient had actually developed "obstructive central" events (**Figure 1C**), which has been seen with glottic closure with BPAP-ST treatment in neuromuscular disease.[9,10] To our knowledge, it has not been reported in primary CSA literature. We hypothesized that over assistance and excessive pressure support with BPAP-ST may draw the $PaCO_2$ below a hypocapnic AT and trigger central apneas. BPAP-ST is not recommended for patients with nonhypercapnic CSA, because pressure support causes greater fluctuations in $PaCO_2$ and further aggravates the ventilatory instability.

ASV targeting 90–95% of calculated ventilation mitigates hyperventilation and hypocapnia by providing a preset minute ventilation or peak flow. ASV not only effectively reduces hyperventilation with a rise of daytime resting $PaCO_2$ in patients with chronic heart failure, but also reduces the sensitivity of CO_2 chemoreceptors and sympathetic nerve activity by slowing respiratory rate and stabilizing respiratory pattern.[11,12] In our case, we cannot distinguish whether beneficial changes in the patient's own chemoreflex sensitivity is by nocturnal ASV therapy or whether it is more of a direct ASV effect to the increase in CO_2. However, we confirm that the ventilation frequency and tidal volume keep in a regular and stable state with ASV treatment, maintaining $PaCO_2$ stable above 40 mm Hg, which is the pivotal factor to eliminate nonhypercapnic CSA. Further studies are required to determine the effectiveness of ASV and the underlying pathogenesis in patients with primary CSA.

CONCLUSIONS

We report a case of nonhypertensive primary CSA in which only ASV mode could stabilize $PtcCO_2$ above the AT (approximately 40 mm Hg) with successfully eliminating central apnea events during manual NIV pressure titration. The possible reason is that ASV can stabilize the ventilation and increase the reduced CO_2 level (within a certain range), rather than simply eliminate the apnea by increasing ventilation. In summary, the level of CO_2 is the determinant of successful NIV pressure titration in patients with nonhypercapnic primary CSA. It is necessary to monitor the CO_2 level, especially if CPAP is unsuccessful.

ABBREVIATIONS

ASV, adaptive servo-ventilation
AT, apneic threshold
BPAP-ST, bilevel positive airway pressure in a spontaneous-timed mode
CPAP, continuous positive airway pressure
CSA, central sleep apnea
EEPAP, end expiratory positive airway pressure
NIV, noninvasive ventilation
$PaCO_2$, arterial partial pressure of carbon dioxide
$PtcCO_2$, transcutaneous partial pressure of carbon dioxide
PDIFF, pressure difference

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DISCLOSURE STATEMENT

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