Chapter 16
Sleep Disordered Breathing at High Altitude

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Clinical Presentation

R. P. is a 64-year-old morbidly obese male (BMI of 30 kg/m^2) with a previous history of hypertension, type 2 diabetes mellitus, and depression who presents to a sleep medicine clinic in Flagstaff, Arizona (6910 feet / 2106 m), where he was vacationing in his timeshare. He was previously diagnosed with non-positional obstructive sleep apnea in Washington D.C. (410 feet / 125 m) 3 years previously. At that time, his split night in-lab polysomnography showed an overall apnea-hypopnea index (AHI) of 27 events/h consisting of only obstructive apneas and hypopneas during a total sleep time of 123 min in the diagnostic portion. Optimal continuous positive airway pressure (CPAP) titration was reached at 12 cmH_2O.

He presents to the sleep medicine clinic in Flagstaff, Arizona, complaining of excessive daytime sleepiness, frequent awakenings with feelings of suffocation at night, and witnessed apneas while wearing his CPAP device. These symptoms are only present during his vacation time in Flagstaff, resolving every time upon returning home (Washington D.C.).

Download of his CPAP device shows that prior to going on vacation, his residual AHI was 2.7 events per hour (only hypopneas) with an average usage of 8 h and 34 min. Over the past 4 days, he has been at Flagstaff, his download shows a

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residual AHI of 23 events/h, with predominately central apneas. He maintained minimal mask leak throughout utilizing a nasal mask interface; however the amount of periodic breathing during the night significantly increased (Fig. 16.1). Overnight oximetry is performed, and results are shown in Fig. 16.2. He is asking what additional treatments can be done to help his symptoms.

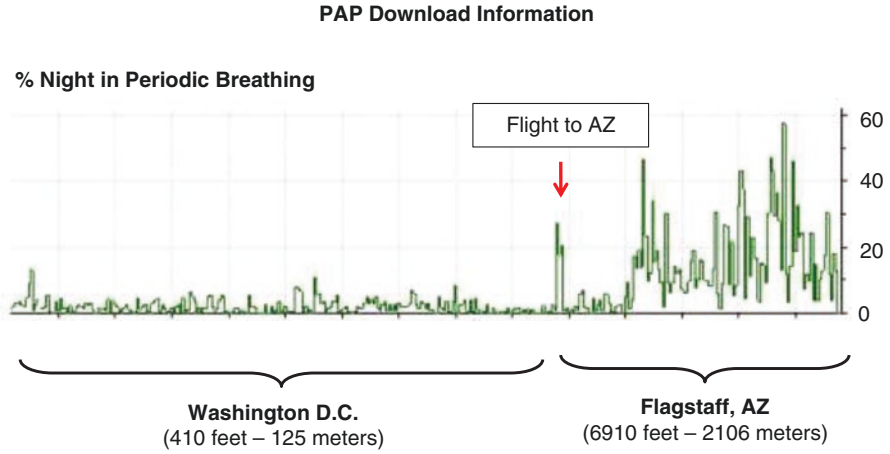

Fig. 16.1 Change in percentage of nocturnal periodic breathing from Washington D.C. to Flagstaff, Arizona, on PAP download

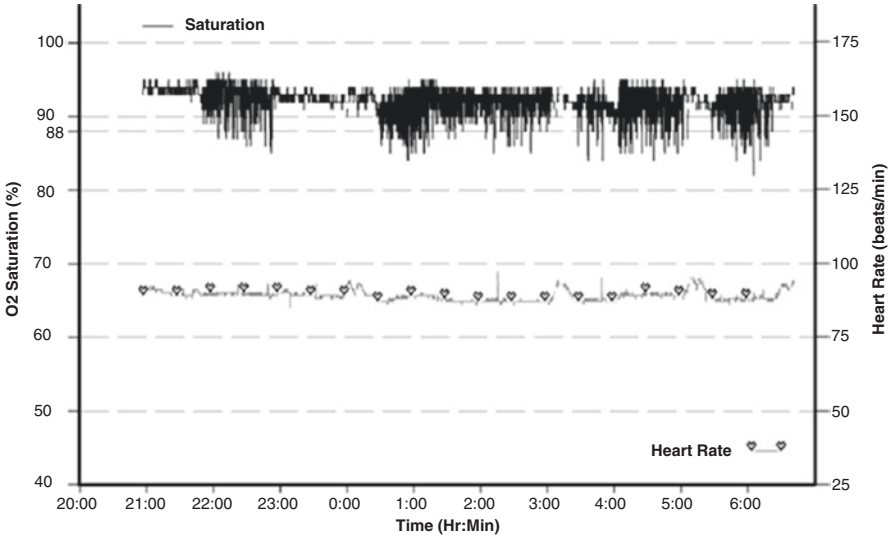

Fig. 16.2 Overnight oximetry obtained after traveling to Flagstaff, AZ, showing frequent oscillatory desaturations

Discussion

High-altitude periodic breathing is characterized by alternating periods of absent respiratory efforts (i.e., central sleep apnea (CSA)) with periods of hyperventilation (hyperpnea) in the absence of other etiologies of periodic breathing (e.g., congestive heart failure with Cheyne-Stokes breathing or intake of narcotics) [1]. High-altitude periodic breathing is a common response to altitude – becoming more common with higher elevations and almost ubiquitous at altitudes >4000 m. There is no level of central AHI that is considered an "abnormal" response. It is the presence of associated symptoms that make the findings of central apneas at altitude considered a disorder. Patients may complain of excessive daytime sleepiness, sleep fragmentation (insomnia), gasping awake, morning headaches, and dyspnea.

The elevation, speed of the ascent, and individual predisposition may play an important role in the pathogenesis of high-altitude periodic breathing. The more rapid the ascent and the higher the altitude, the greater the risk of developing periodic breathing. Descending to a lower altitude will often relieve central apneas [2]. Periodic breathing may develop during ascension, immediately after or during the acclimatization period. Few individuals exhibit periodic breathing at altitudes as low as 1500 m (4900 feet), while up to 25% will develop it at 2500 m (8202 feet), and as mentioned, virtually everyone at 4000 m (13,000 feet) will develop some degree of high-altitude periodic breathing [3]. Periodic breathing can also be observed in those individuals chronically living and acclimatized to high altitude (i.e., highlanders). In comparison to individuals living at sea level, highlanders living at an altitude of 3825 m have a greater prevalence of sleep apnea (77% vs 54%, $p < 0.001$), as well as a twofold increase in sleep apnea severity, largely explained by increased frequency of central rather than obstructive events [4].

Pathophysiologic effects of high altitude relate to changes in barometric pressure and subsequent changes in the ambient pressure of oxygen. Since the fraction of inspired oxygen remains constant at approximately 21% during ascension, the most important determinant of arterial oxygen tension (PaO_2) at any altitude is the barometric pressure. For example, at an altitude of 3000 m, the barometric pressure and inspired atmospheric partial pressure of oxygen is only about 70% of that at sea level. As PaO_2 falls due to a low atmospheric pressure (hypobaric hypoxia) upon ascension, ventilation will be stimulated resulting in hypocapnia and respiratory alkalosis. The magnitude of the ventilatory response increases with increasing altitude and progresses over days after ascension. It is this hyperventilation triggered by hypoxia, with subsequent fall in arterial carbon dioxide ($PaCO_2$) below the apneic threshold, that results in central apneas [5]. With breathing cessation, increased $PaCO_2$ will trigger a subsequent hyperventilation period with high tidal volumes, in which the PaO_2 rises and $PaCO_2$ falls to near wakefulness level, perpetuating the respiratory oscillation (periodic breathing). Even though acclimatization to high altitude results in an overall increase in saturation of oxygen (SpO_2), periodic breathing may still increase in duration and persist in time as a result of the

progressive increase in the respiratory control system response to hypoxia and hypercapnia (i.e., a high loop gain) [1, 6, 7].

Sex differences in the propensity for high-altitude periodic breathing have been noted. Women stabilize their respiration at high altitude more quickly than do men and demonstrate less proclivity for central apneas [17]. It is thought that women may be protected due to the effect of estrogen and/or progesterone; however, the exact mechanism remains unclear. Women may have a blunted hypoxic ventilatory response that protects them against hyperventilation and subsequent hypocapnia-induced central apneas (i.e., lower loop gain). In addition, heritable genetic variability in ventilatory chemo-responsiveness has been shown, though whether the propensity for developing high-altitude periodic breathing is also inherited is unknown [4]. Persons who have developed high-altitude periodic breathing in the past are more likely to have recurrence upon re-ascension, and therefore these patients deserve prophylactic therapies and closer follow-up.

On polysomnography, central apneas occur during non-rapid eye movement (NREM) sleep while being largely absent during rapid eye movement (REM) sleep. This is thought to be due to the fact that the primary driver of ventilation during NREM sleep is chemo-responsiveness, while hypoxic and hypercapnic responsiveness is blunted during REM sleep. Central apneas are generally short (cycles lengths <40 s) in high-altitude periodic breathing, unlike that seen with Cheyne-Stokes respiration related to heart failure. Sleep is often disrupted, though overall total sleep time and REM time may be preserved.

Among patients with known obstructive sleep apnea (OSA), exposure to high altitude may cause worsening of sleep disordered breathing by worsening obstructive events or by inducing central events [8, 9]. Independent of sex, patients with cardiovascular disease are at increased risk for obstructive sleep apnea and central sleep apnea at high altitude [10]. In lifelong altitude residents with severe pulmonary hypertension associated with excessive erythrocytosis (i.e., chronic mountain sickness), central and obstructive apneas, as well as nocturnal hypoxemia, have shown to be more severe compared with healthy high-altitude dwellers [2]. In patients with OSA who travel to high altitude (e.g., 2750 m), their home positive airway pressure (PAP) settings may be inadequate to treat their obstructive sleep apnea. Although application of positive airway pressure is associated with decreased central sleep apnea and hypoxemia that occurs with altitude, baseline PAP settings may be suboptimal to completely eliminate OSA, resulting in higher sleep apnea severity and sleep fragmentation [11]. The fan speeds in CPAP machines need to adjust for barometric pressure change in order to keep the delivered CPAP pressure consistent at different altitudes. Newer machines are able to automatically adjust to altitude, while older machines need to be manually adjusted.

In the above clinical case, it appears the patient's sleep-related symptoms emerge in Flagstaff, Arizona. The altitude of Flagstaff, Arizona, is 2106 m in comparison to the altitude of Washington D.C at 125 m. By physiologic adaptation of oxygen content and oxygen carrying capacity to high altitude, slow ascent can decrease respiratory drive triggered by hypoxia. Therefore, slow ascension and subsequent acclimatization are among several interventions to ameliorate the development of

sleep related breathing disorders. Unfortunately, at elevations above 3500–4000 m, acclimatization alone does not restore normal sleep or prevent the development of CSA. There are a few evidence-based options to treat this patient. If descending from high altitude is not an option, adjunctive treatment with acetazolamide and/or oxygen has been proven to be effective measures; however, availability, side effects, and limitations of the intervention should be cautiously considered.

Acetazolamide improves sleep apnea at high altitude by inducing a metabolic acidosis and behaving as a respiratory stimulant. Acetazolamide has shown to decrease AHI, decrease percentage of periodic breathing time, and increase nocturnal oxygenation in patients with high-altitude periodic breathing [12]. In the current literature, acetazolamide dosing has ranged anywhere from a daily dose of 250–750 mg; however, prophylactic dose of 125–250 mg by mouth twice daily is currently recommended to be started anywhere from 1 to 3 days prior to ascent [13, 14]. If the patient has a previously diagnosed sleep disorder, it is highly encouraged to continue PAP therapy while at high altitude [13]. Data has shown that patients with OSA who spend 3 days at moderately elevated altitude, a combination of both acetazolamide and auto-CPAP, compared with auto-CPAP alone, was superior at improving nocturnal SpO_2 and AHI [15]. Alternatively, because hypoxia is the main mechanism driving periodic CSA at high altitude, supplementing oxygen (1–2 L/min, or at a rate that results in $SpO_2 > 90\%$) to CPAP may suppress high-altitude periodic CSA in patients with obstructive sleep apnea [3]. In a small study of previously healthy individuals, supplemental oxygen alone was shown to be superior to adaptive servo-ventilation (ASV) in periodic breathing at high altitude [16]. When feasible, however, descending from altitude is always the treatment of choice.

As in our patient, it may be beneficial to obtain download data in patients who are not acclimatized to taking short trips at high altitudes [14]. A brief download of the patient's PAP device at high altitude can delineate what types of events are happening (e.g., uncontrolled OSA vs emergent CSA). If there is underlying lung disease present, a high-altitude simulation test can be performed to determine if the patient needs supplemental oxygen. At the current time, there is no mechanism to perform a simulated high-altitude polysomnogram unless the sleep center is at the desired altitude where the patient will be traveling. For patients who live at altitude and are getting sleep studies at sea level, a false-negative study may result since AHI decreases significantly with descent [17]. Although there are no guidelines or consensus regarding adjustment of PAP therapy during ascension, it is important to recommend PAP adherence to individuals with OSA who travel to and sleep at higher altitudes. Current data support that baseline PAP settings may be inadequate to eliminate hypopneas at high altitude. Although we may speculate that variable pressure or auto-PAP devices might adequately treat OSA at high altitude, decisions regarding escalation of PAP therapy for such patients may need to be made on a case-by-case basis based on suspected predominant type of breathing disorder. The addition of low flow oxygen entrained into the PAP device may also be considered based on feasibility and availability of location.

In addition to periodic breathing at high altitude, there is also a growing body of literature on acute mountain sickness (AMS) and the benefit of CPAP therapy. AMS

happens typically when a fall of barometric pressure upon ascension results in hypoxia-driven symptoms such as high-altitude cerebral edema with altered mental status, headache, ataxia, fatigue, nausea, vomiting, and high-altitude pulmonary edema (HAPE). It should be noted that high-altitude periodic breathing is *not* the same as nor a form of acute or chronic mountain sickness (Table 16.1). Periodic breathing is a common response to altitude that affects virtually all persons at >4000 m [18]. Whether proclivity or severity of periodic breathing predicts or predisposes to AMS has been evaluated. The AHI that results from high-altitude periodic breathing does not differ between those who do and do not develop AMS at >4000 m. However, those who develop AMS tend to have markedly worse nocturnal and wake SpO_2. It is unclear whether high-altitude sleep-breathing disorder contributes to the development of AMS in some individuals, or whether periodic breathing and hypoxemia develop because of the development of HAPE. The current data suggest the latter. It has been suggested that high-altitude periodic breathing may even be protective from AMS and HAPE, since those who readily develop high-altitude periodic breathing have greater hypoxic ventilatory response [8]. This robust hypoxic ventilatory response prevents exaggerated or prolonged oxygen desaturations that would be seen with acute or chronic mountain sickness. In any case, individuals who have a history of periodic breathing or AMS/HAPE are at risk

Table 16.1 Notable differences in acute and chronic mountain sickness

	Acute mountain sickness	Chronic mountain sickness
Timing	Onset within hours and lasts days	Months to years
Altitude	>2400 m	>2500 m (long-term residents)
Symptoms	Headache, dizziness, palpitations, insomnia, loss of appetite, nausea, altered mental status, lightheaded, hallucinations	Cyanosis, malaise, fatigue, exercise intolerance, vein dilation, headache, tinnitus, paresthesia, sleep disturbances
Mechanism	Relative hypoventilation, impaired gas exchange, fluid retention and redistribution, and increased sympathetic drive [20, 21]	Maladaptive ventilator response to high altitude (impaired hypoxemic ventilatory response), abnormal baroreceptor-mediated control of vascular resistance and hypoxemia driven erythropoiesis [22–24]
Complications	High-altitude pulmonary edema, High-altitude cerebral edema, death	Pulmonary hypertension, polycythemia, right ventricular hypertrophy, right heart failure, neuropsychiatric symptoms, peripheral arterial pressure falls, death
Treatment	Descend from altitude, acetazolamide	Descend from altitude, mild exercise, acetazolamide, almitrine, enalapril, medroxyprogesterone
Prevention	Acetazolamide, dexamethasone, ibuprofen, acclimatization, benzodiazepines, avoid smoking and alcohol	None studied

for recurrence upon re-ascension and will benefit from prophylactic treatment. As mentioned, acetazolamide and supplemental oxygen may help with periodic breathing and can also help prevent high-altitude pulmonary edema. Likewise, dexamethasone prior to ascension decreases the likelihood of AMS and HAPE. Dexamethasone may alter sleep architecture but has not shown to change overall periodic breathing AHI [18]. Finally, CPAP therapy is used for high-altitude periodic breathing and may also provide benefit for AMS, likely via improving oxygenation. CPAP use intermittently during wake and during sleep at altitude improved symptoms of AMS and decreased occurrence of HAPE [19].

Clinical Pearls

- Periodic breathing and central sleep apnea develop commonly upon ascending to high altitude due to low barometric pressure resulting in hypobaric hypoxemia due to decreased partial pressure of oxygen.
- Patients with obstructive sleep apnea who were previously asymptomatic may develop daytime sleepiness, sleep fragmentation (insomnia), and sense of dyspnea secondary to worsening OSA, or emergence of high-altitude related periodic breathing.
- If descending from high altitude is not feasible, treatment of symptomatic periodic breathing that develops at altitude includes acetazolamide, continuation of PAP therapy for previously diagnosed sleep disordered breathing, and oxygen supplementation at 1–2 L/min.
- ASV therapy has not been shown to be superior to oxygen supplementation in central sleep apnea due to high-altitude periodic breathing.
- Despite limited published data, acetazolamide therapy is recommended prophylactically for those susceptible to periodic breathing at high altitude at a dose of 125–250 mg by mouth twice daily to be started about 1–3 days prior to ascension.

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