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Lung Disease at High Altitude

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Abstract

Large numbers of people travel to high altitudes, entering an environment of hypobaric hypoxia. Exposure to low oxygen tension leads to a series of important physiologic responses that allow individuals to tolerate these hypoxic conditions. However, in some cases hypoxia triggers maladaptive responses that lead to various forms of acute and chronic high altitude illness, such as high-altitude pulmonary edema or chronic mountain sickness. Because the respiratory system plays a critical role in these adaptive and maladaptive responses, patients with underlying lung disease may be at increased risk for complications in this environment and warrant careful evaluation before any planned sojourn to higher altitudes. In this review, we describe respiratory disorders that occur with both acute and chronic exposures to high altitudes. These disorders may occur in any individual who ascends to high altitude, regardless of his/her baseline pulmonary status. We then consider the safety of high-altitude travel in patients with various forms of underlying lung disease. The available data regarding how these patients fare in hypoxic conditions are reviewed, and recommendations are provided for management prior to and during the planned sojourn.

With the growing interest in adventure travel, increasing numbers of people are traveling to high altitude (>2000 m), where the defining environmental feature is hypobaric hypoxia. Exposure to low oxygen tension sets in motion a series of important physiological responses that allow individuals to adapt to and tolerate the hypoxic conditions. In some cases, maladaptive responses predispose affected individuals to various forms of acute and chronic high-altitude illness. Owing to the critical role played by the respiratory system in these adaptive and maladaptive responses, individuals with underlying lung disease may have increased risk of developing complications in a hypobaric hypoxic environment. Thus, careful evaluation before planned excursions to a high altitude may be justified. This review considers these issues in greater detail. We review respiratory disorders that occur with both acute and chronic exposures to high altitude. These disorders may affect any person who ascends to high altitude, regardless of his/her underlying pulmonary status. In addition, we address the safety of high-altitude travel in patients with underlying lung disease, including

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pulmonary vascular disorders, obstructive and restrictive diseases, and ventilatory control disorders. For each form of underlying pulmonary disease, we review the available data regarding how these patients fare in hypoxic conditions, consider other theoretical risks of high-altitude exposure and propose recommendations for managing a planned sojourn to high altitude.

Environmental factors at high altitude

Several important features of the high-altitude environment have the potential to affect both healthy individuals and those with pre-existing lung disease. Barometric pressure decreases in a nonlinear manner with increasing elevation. At any given elevation, barometric pressure varies based on the latitude and time of year, but at the elevations visited by most tourists, the effect of such changes is likely to be small [1]. As a result of the lower barometric pressure, the inspired partial pressure oxygen (P_iO_2) falls, leading in turn to decreased alveolar and arterial oxygen tensions (P_AO_2 and P_aO_2, respectively).

With increasing altitude, air density, humidity and temperature also decrease. These factors may contribute to airway reactivity, insensible water losses, ventilatory changes and alterations in pulmonary hemodynamics. High altitude also features a reduced allergen burden, including dust mites, a common trigger for asthma [2]. Changes in air quality are equivocal at high altitude. While one might expect pollution to decrease with movement away from cities to the mountains, this may not be the case. Mountain valley systems have the ability to trap pollution from urban areas, heavily traveled regions near roads may be prone to the accumulation of heavy-duty automotive emissions [3], and local air quality in developing countries is often poor due to smoke from wood- and animal dung-burning stoves used by local residents and proprietors of lodges [4].

Changes in pulmonary physiology at high altitude

Acute exposure to hypoxia causes several critical changes in respiratory physiology that affect all individuals who travel to high altitude, regardless of whether they have underlying lung disease. Upon ascent to high altitude, the low P_aO_2 leads to an increase in minute ventilation, known as the hypoxic ventilatory response (HVR). Mediated by the carotid bodies, the HVR varies in magnitude among individuals and serves to increase P_AO_2 and P_aO_2 [5]. HVR also causes a decrease in the arterial partial pressure of carbon dioxide (P_aCO_2); the resulting respiratory alkalosis leads to a leftward shift of the oxyhemoglobin dissociation curve, which improves alveolar oxygen uptake and – to a lesser degree – impairs oxygen delivery to the tissues. This leftward shift is balanced by increased production of 2,3-diphosphoglycerate by red blood cells after ascent to high altitude, a mechanism that in turn creates a compensatory rightward shift in the curve, so that on balance the *in vivo* P_{50} remains about the same as that at sea level [6].

Hypoxic pulmonary vasoconstriction (HPV) is another important physiologic response to acute hypoxic exposure. Mediated by decreased alveolar oxygen tension, this response – which also varies among individuals – increases pulmonary vascular resistance and pulmonary artery pressure (PAP) [7,8]. As will be discussed later, this mechanism plays a

pivotal role in the pathophysiology of both acute and chronic forms of high-altitude illness [9,10].

Respiratory disorders associated with acute exposure to high altitude

High-altitude pulmonary edema

By far, the most important respiratory disorder associated with acute (hours to days) high-altitude exposure is high-altitude pulmonary edema (HAPE). HAPE is a noncardiogenic pulmonary edema that may occur in unacclimatized persons within 2-4 days of ascent to altitudes above 2500 m. In its early stages, it is characterized by increasing exercise intolerance and a dry cough, while in advanced cases individuals develop dyspnea at rest, cyanosis and a cough productive of pink, frothy sputum [11]. HAPE may occur as an isolated problem or in conjunction with either acute mountain sickness (AMS) or high-altitude cerebral edema (HACE). Clinical findings include tachycardia, tachypnea, low-grade fever, hypoxemia, and unilateral or bilateral inspiratory crackles. When available, chest radiography demonstrates patchy bilateral alveolar opacities although, in early HAPE, findings may be focal and occur predominantly in the right middle lobe [12].

Risk factors for HAPE include a prior history of the disorder, male gender, rapid ascent, higher altitudes, pre-existing respiratory infection and intense exercise [13-17]. In addition, HAPE susceptibility is associated with a blunted HVR [18-20]. While HAPE often affects otherwise healthy individuals, the risk for this disorder may be elevated in persons with underlying pulmonary hypertension (PH), as numerous reports in the literature document its occurrence in patients with PH due to a variety of causes, including unilateral absence of pulmonary artery [21], Down's syndrome [22], granulomatous mediastinitis [23] and previous anorexigen use [24].

The pathophysiology of HAPE is complex, and more comprehensive discussions can be found elsewhere [25]. In short, susceptible individuals develop exaggerated HPV and a large rise in PAP when exposed to hypoxia. As these changes are distributed unevenly within the pulmonary vascular bed, regional overperfusion of capillaries occurs, leading to ‘stress failure’ of the blood-gas barrier, increased permeability and pulmonary edema [26]. This process, which is noninflammatory in nature, may be accelerated by impaired alveolar fluid clearance [27].

While several modalities are available for HAPE prophylaxis (Table 1), gradual ascent to high elevations remains the best method to prevent HAPE. Although these recommendations have never been subjected to formal study, expert opinion generally holds that above 3000 m individuals should not increase their sleeping elevation by more than 300-500 m per night, and should include a rest day every 3-4 days to facilitate acclimatization. Persons with a prior history of HAPE should also strongly consider the use of pharmacologic prophylaxis. By virtue of its pulmonary vasodilatory properties, nifedipine has been the mainstay of prevention for many years [13], but recent evidence suggests that the phosphodiesterase-5 (PDE-5) inhibitor tadalafil may also play a role in this regard [28]. Sildenafil works by a similar mechanism and may also prove to have a similar benefit, but no published controlled trials have yet examined its role in HAPE prevention at high altitude. Data also support a

potential role for inhaled salmeterol, based on its ability to improve alveolar fluid clearance [27], but this medication has not yet become part of standard protocol and should not be used alone for HAPE prophylaxis. Interestingly, acetazolamide and dexamethasone, agents commonly used in the prevention of AMS and HACE, may also prove to be beneficial in the prevention of HAPE. Maggiorini *et al.* demonstrated that dexamethasone reduces the risk of HAPE in susceptible individuals; the mechanism of this observed benefit is not clear but may be related to alterations in capillary permeability [28]. Acetazolamide has been shown to mitigate HPV and blunt the increase in PAP with hypoxic exposure in animal studies [29-31]. A single study suggests that this drug may also blunt HPV in humans, but randomized trials have yet to establish a role for acetazolamide in HAPE prevention of treatment [32].

Appropriate treatment of HAPE depends on the location in which it occurs, and may include a combination of methods (Table 2). Individuals who develop HAPE near a readily accessible medical facility may be treated with supplemental oxygen and observation at the same altitude. When HAPE occurs in more remote locations away from medical care, as is often the case, immediate descent is indicated and usually leads to resolution of the problem. If descent is not feasible due to weather or other factors, supplemental oxygen should be administered, or the individual may be placed in a portable hyperbaric chamber to simulate descent to a lower elevation. Nifedipine may be added to the treatment regimen and may even be effective alone if the above definitive interventions are not available [33]. Anecdotal reports suggest that inhaled β-agonists are being used for field treatment [34], but there is no formal evidence demonstrating benefit from this strategy. Efforts should be made to limit physical exertion on the part of affected individuals, as this may lead to increased PAP and worsening edema.

Pulmonary dysfunction in AMS

Acute mountain sickness is far more common at altitude than HAPE, affecting between 25 and 50% of unacclimatized low-landers ascending to altitudes between 2000 and 4200 m [35, 36]. Characterized by the presence of headache in combination with malaise/fatigue, insomnia, dizziness or gastrointestinal symptoms (nausea, vomiting or anorexia) [37], AMS is thought to be a neurologically mediated process. However, there is evidence that pulmonary dysfunction may contribute to the underlying pathophysiology. Several studies suggest that arterial hypoxemia during the first few hours of exposure to the hypoxic environment of simulated or actual high altitude may predispose individuals to the development of AMS [38, 39]. Other evidence suggests that individuals with impaired HVR may also be at increased risk for AMS, although the data have not been consistent in this regard [39-43]. Bärtsch *et al.* demonstrated that, although patients who develop AMS at high altitude have normal HVR at sea level, they may experience an impaired increase in ventilation during ascent to higher elevation when compared with healthy controls [39].

Those who develop AMS at high altitude also have a more severe degree of hypoxemia and a larger alveolar-arterial oxygen difference than those without AMS [39,44,45]; these abnormalities appear to correlate with AMS severity [39,46]. In addition, Ge *et al.* demonstrated a blunted increase in carbon monoxide diffusing capacity in patients with

AMS compared with healthy counterparts [45]. Other studies have provided indirect evidence of increased extravascular lung water in healthy individuals and those with AMS at high altitude [47-49]. Grissom *et al*. demonstrated that, in patients with AMS, acetazolamide improves symptoms, decreases hypoxemia and prevents the progression of pulmonary dysfunction [38].

Periodic breathing

Periodic breathing, alternatively referred to as Cheyne-Stokes respirations, is a form of sleep-disordered breathing that occurs frequently in visitors to altitudes above 2000 m, and is almost universal after rapid ascent to elevations above 4000 m, even in the absence of acute altitude illnesses such as AMS or HAPE. It is marked by a crescendo-decrescendo pattern in tidal volume, punctuated by periods of apnea that can last anywhere from 5 to 20 s. This is a centrally mediated process with a pathophysiology distinct from that of the more commonly seen obstructive sleep apnea (OSA). People experiencing periodic breathing often report restless sleep, racing thoughts and frequent nocturnal arousals, often with a distinct feeling of suffocation. Apneic periods are characteristically followed by 'bursts' of increased ventilation, possibly coinciding with arousals due to air hunger. Formal studies of this phenomenon have noted the presence of disrupted sleep architecture with a decreased amount of deep sleep (stage III and IV rapid eye movement) [50,51], severe arterial hypoxemia, and wide fluctuations in nocturnal oxygen saturation (S_aO_2) [52]. Despite impaired sleep quality, total sleep time is largely unaffected. With acclimatization to moderate and even very high altitudes (>5000 m), sleep quality generally improves, although periodic breathing can persist in some cases for long periods of time, particularly at very high elevations [53,54]. The literature suggests that the percentage of time spent in periodic breathing during sleep increases with increasing altitude [55].

The occurrence of periodic breathing at high altitude has been strongly linked to HVR [56,57]. It has been postulated that in individuals with a vigorous HVR, periodic breathing helps to maintain nocturnal oxygenation, conferring an advantage to these persons in their tolerance of high altitude [58]. Evidence also suggests that an exaggerated ventilatory response to hypercapnea also plays a central role in the pathophysiology of this process [59].

Medications such as acetazolamide and theophylline reduce the incidence of periodic breathing, although the latter is not commonly used for this purpose at high altitude owing to its narrow therapeutic window and potential for drug interactions [60-62]. Other agents used for sleep at sea level – such as temazepam, loprazolam, zolpidem and zaleplon – have been shown to improve sleep quality at high altitude but have no consistent effect on the incidence of periodic breathing [63-68]. Beyond these pharmacologic options, oxygen enrichment of sleeping quarters has also been shown to increase the percentage of time spent in deep sleep stages, improve subjective sleep quality and decrease next-day AMS scores [69,70].

Respiratory disorders associated with chronic exposure to high altitude

As a result of maladaptive responses to chronic (months to years) hypobaric hypoxia, up to 5-10% of high-altitude residents in certain areas of the world develop one out of two forms

of chronic high altitude illness – chronic mountain sickness (CMS) and high-altitude pulmonary hypertension (HAPH) [71]. Important regional and ethnic differences may influence susceptibility to these illnesses; the disorders are often seen in both Andean natives and Han Chinese emigrants to the high-altitude Tibetan plateau, but are relatively rare occurrences in the Tibetan and Sherpa peoples, who have been living at a high altitude for significantly longer periods of time [72-75].

CMS

Initially described in natives of the Peruvian Andes, CMS – also known as Monge's Disease – occurs in people residing at elevations above 2500 m for 1 or more years. This condition is marked by the presence of polycythemia (hemoglobin >19 g/dl in females or >21 g/dl in males), chronic hypoxemia and neurologic symptoms, including migraine headaches, lethargy, irritability, impaired concentration and acral paresthesias. Diagnostic criteria also require the absence of underlying lung disease that could pre-dispose to the development of hypoxemia and polycythemia [71]. Although CMS patients may develop PH and right heart dilation, heart failure is rare [76]. The symptoms of CMS usually disappear with travel to lower altitudes but recur upon reascent [77]. Notably, CMS is more common in men and postmenopausal women, possibly owing to the absence of a progesterone-mediated contribution to ventilatory drive [78,79].

Chronic mountain sickness probably occurs due to maladaptive ventilatory responses to high altitude and subsequent hypoxia-driven erythropoiesis. When compared with healthy high-altitude residents, persons with CMS demonstrate impaired HVR [80], abnormal baroreceptor-mediated control of vascular resistance [81] and more frequent headaches [82]. Polycythemia, hypoxemia and CMS severity correlate with advancing age among high-altitude residents [82], suggesting that the natural age-associated decrease in ventilation [83] may contribute to the development of CMS.

Treatment for CMS includes relocation to a lower altitude, periodic phlebotomy [84], isovolemic hemodilution [85,86] or supplemental oxygen [87]. The long-term use of respiratory stimulants, such as medroxyprogesterone [88] or acetazolamide [89-91], also improves oxygenation and polycythemia in CMS patients. Angiotensin-converting enzyme inhibitors such as enalapril may also be helpful [92,93].

HAPH

Previously referred to as high-altitude heart disease [94,95], hypoxic cor pulmonale and infantile/adult subacute mountain sickness [96], HAPH is characterized by right ventricular (RV) enlargement and PH in the absence of polycythemia or neurologic dysfunction [95]. HAPH is generally seen in long-term residents of altitudes above 2500 m but has been described in Indian soldiers posted to high elevations for periods of weeks to months [96]. Histologically characterized by muscularization and medial hypertrophy of distal pulmonary arteries and arterioles [97,98], HAPH appears to be more common in women and children [99]. Affected individuals typically develop dyspnea, cyanosis, peripheral edema, hepatomegaly and exercise intolerance.

Symptoms of right heart failure may occur in up to 47% of patients with HAPH [100]. Published reports demonstrate evidence of PH (mean PAP >30 mmHg or systolic Pap >50 mmHg), RV hypertrophy/enlargement and hypoxemia [71]. Formal diagnosis of HAPH requires the absence of polycythemia, chronic obstructive or interstitial lung disease, and other causes of PH [71].

As with CMS, the symptoms of HAPH disappear with descent to lower altitudes. Nifedipine has been shown to decrease PAP in high-altitude residents [101], but studies in HAPH patients are limited. Subsequent investigations have indicated that the PDE-5 inhibitors sildenafil and tadalafil may also mitigate altitude-mediated PH [28,102]. Aldashev *et al.*, for example, demonstrated the efficacy of sildenafil at decreasing PAP in individuals with proven HAPH [103], but this and other studies have yet to examine the long-term effects of these agents on disease progression.

Chronic lung disease at high altitude

Among the multitude of people traveling to high altitude for work or pleasure, there are likely many individuals with underlying lung diseases such as asthma or chronic obstructive pulmonary disease (COPD). While these persons may face the same risk of acute altitude illness as otherwise healthy individuals, it is also necessary to consider whether hypobaric hypoxia and other features of the high-altitude environment might adversely affect their underlying pulmonary disease and predispose them to significant complications. The literature on this issue is, unfortunately, limited to a few systematic studies and case reports, but by carefully considering this body of evidence and current knowledge of the pathophysiology in each disease process, it is possible to draw tentative conclusions about the safety of travel to high altitude in these individuals.

Pulmonary vascular disorders

PH—Pulmonary hypertension may occur as a primary disorder or as a result of other disease processes, such as obesity hypoventilation syndrome or COPD. While studies have not yet systematically investigated the effects of high-altitude travel on those with pre-existing PH, the critical role of increased PAP and pulmonary vasoreactivity in the pathogenesis of HAPE suggests that patients with PH may face an increased risk of HAPE with ascent to high altitude. Indeed, the literature contains numerous cases of HAPE in patients with underlying PH secondary to congenital absence of one pulmonary artery [21,104], pulmonary artery occlusion from granulomatous mediastinitis [23], pulmonary embolism [105], Down's syndrome [22], anorexigen use [24] and various congenital cardiac abnormalities [106]. These can act as independent risk factors or in combination, as described in a recent case report [107]. While HAPE typically occurs at altitudes above 2500 m in otherwise healthy individuals, some patients with underlying PH have developed HAPE at significantly lower elevations of 1500-1750 m [22,104].

Beyond susceptibility to HAPE, patients with PH may also be at risk for other complications, including worsening RV function, ischemia and worsening hypoxemia. Any further increase in PAP that occurs due to HPV following ascent could increase RV afterload and contribute to worsening function or RV dilation, thereby decreasing

subendocardial blood flow and leading to ischemia and chest pain. Finally, patients with right-to-left intracardiac shunt may become more hypoxemic at high altitude as the increase in PAP increases flow across the shunt.

Long-term residence at high altitude should be avoided in patients with underlying pH, as the chronic alveolar hypoxia will exacerbate their underlying disease. In fact, one of the standard recommendations for people who develop PH of any underlying cause while living at high altitude is to relocate to a lower elevation.

The precise level of PH that predisposes to these problems is not known, as baseline pulmonary artery pressures in the case reports noted previously vary to a considerable degree. The safest strategy is for PH patients to avoid high-altitude travel to even moderate altitudes (>2000 m). As this may not be feasible in all situations (travel may be unavoidable or strongly desired), the following are tentative recommendations for management of the patient with PH who wishes to travel to such elevations. Patients with a mean PAP over 35 mmHg or systolic PAP over 50 mmHg at sea level who seek to travel to altitudes above 2000 m should travel with supplemental oxygen to blunt HPV upon ascent. Those patients not on a regimen of pulmonary vasodilators should consider sustained-release nifedipine, tadalafil or sildenafil for the duration of their sojourn at high altitude. Whichever agent is chosen, it should be proven to improve symptoms or decrease PAP in these patients at their resident altitudes. Patients with PH and mean PAP under 35 mmHg or systolic PAP under 50 mmHg should also consider avoiding high-altitude travel if possible. If they do travel to high altitude, these person should consider prophylactic nifedipine or tadalafil for the duration of their sojourn, or supplemental oxygen as an alternative. Both medications treat PH and prevent HAPE. All patients, regardless of the severity of their PH, should be counseled regarding the recognition and management of HAPE and other complications, with a particular emphasis on the importance of a slow ascent.

Thromboembolic disease—Although a large number of case reports document the occurrence of venous thromboembolism at high altitude, systematic studies have not established an increased risk of venous thromboembolic events (VTEs) in this environment. A retrospective study by Anand *et al.* found an increased incidence of VTE (odds ratio: 30.5) at military hospitals in high-altitude regions, compared with low-altitude areas [108]. However, this study population largely consisted of long-term residents of these regions (mean duration of residence >10 months), thus these data cannot be extrapolated to thes risk of short-term travelers to high altitude [108]. Other studies have examined the effect of hypoxia on various markers of the coagulation system as surrogate markers for the risk of coagulopathy but have not yielded consisitent evidence of a hypercoagulable state at high altitude [4].

While high-altitude exposure may not influence the risk of VTEs in all individuals, it may affect patients with an underlying coagulation disorder. In many of the case reports of VTEs at high altitude, the patient was subsequently diagnosed with a hypercoagulable state, such as hyperhomocysteinemia [109], protein C deficiency [110] or sickle cell hemoglobinopathy [111]. Schreijer *et al.* studied 71 healthy subjects during an 8-h flight with cabin pressure equivalent to an altitude of 1800-2100 m, demonstrating increases in thrombin-antithrombin

complexes compared with responses of the same subjects to nonhypoxic control scenarios. Notably, those patients with underlying Factor V Leiden who used oral contraceptives, a known risk factor for VTE at low altitude, were found to have the largest increases in thrombin-antithrombin complexes after the simulated latitude of air travel [112].

In the absence of further systematic trials examining this issue, it is difficult to conclude with any degree of certainty that high-altitude exposure increases the risk of VTE in patients with an underlying hypercoagulable state. Nevertheless, the available evidence suggests that these individuals should at least be vigilant about preventing and monitoring for this problem during high-altitude travel. Those persons already on an anticoagulation regimen should remain on these medications during their sojourn. If on warfarin, patients should have close monitoring of international normalized ratio before and after travel to high altitude, as changes in altitude may be associated with a subtherapeutic international normalized ratio [113]. Consideration should be given to using low-molecular-weight heparin instead of warfarin during high-altitude travel, as the anticoagulation effects disappear more quickly with cessation of the medication if the patient develops bleeding complications. Whil the clinical correlates of the findings by Schreijer *et al.* are unknown [112], patients with a history of VTE or hypercoagulable disorder may consider discontinuing oral contraceptives before traveling to high altitude, if such a decision is feasible. In addition, all patients, regardless of their risk for thromboembolic disease, should be advised to avoid dehydration, venous occlusion and prolonged immobility, as these factors may elevate the risk for VTE.

Obstructive lung disease

COPD—Chronic obstructive pulmonary disease, an exceedingly common respiratory disorder, is characterized by impaired gas exchange, airway obstruction and increased work of breathing. Exposure to hypobaric hypoxia at high altitude may alter these factors, possibly exacerbating the baseline disease state. As only a single study has examined COPD patients at terrestrial high altitude, much of the insight into this issue comes from the literature on the safety of commercial air travel in patient with COPD, as in-flight cabin pressures are such that individuals may be exposed to equivalent altitudes as high as 2438 m (8000 ft).

With regards to gas exchange, the literature clearly demonstrates that COPD patients experience worsening hypoxemia when exposed to a hypobaric hypoxic environment. In the lone study of these patients performed at terrestrial altitude, Graham and Houston demonstrated a fall in a P_aO_2 from 66 ± 7 mmHg to 52 ± 7 mmHg in eight COPD patients (mean forced expiratory volume at 1 s [FEV_1]:1.27 l) within 3 h of ascent to 1920 m [114]. Similar decreases in P_aO_2 have been shown in the setting of simulated altitude and commercial air travel in COPD patients with a mean FEV1 of 1.0-1.5 l, with oxygenation worsening even further upon mild exertion [115-118]. It should be noted, however, that the literature is limited by the fact that these studies did not include patients with milder disease or carbon dioxide retention, and no systematic trial has examined individuals in conditions equivalent to altitudes above 3050 m.

In many of the studies, noted, the mean P_aO_2 fell to levels near or below 50 mmHg during exposure equivalent to 2440 m. This threshold is important, as it is considered by both the American Thoracic Society [119] and British Thoracic Society [120] as the minimum P_aO_2 to be maintained in a patient with COPD during commercial air travel. It should be recognized, however, that the cut-off used by these organizations is arbitrary and not based on data showing worse outcomes in patients who P_aO_2 falls below these levels during commercial flight. While not all patients are symptomatic with a P_aO_2 of less than 50 mmHg, it is recommended that patients who cannot maintain oxygenation above this threshold use supplemental oxygen during flight. AS these thresholds have become standard practice for commercial flight, it is reasonable to consider whether they should be applied to high-altitude travel as well. Notably, in the majority of studies of COPD patients during actual or simulated commercial flight, few patients experienced increased symptoms of severe complications as a result of the increased hypoxemia. In addition, these studies generally involved short exposures lasting only hours, while many high-altitude sojourns may actually last days to weeks, allowing time for ventilatory acclimatization, which may increase P_aO_2 to levels above the 50 mmHg threshold.

If one opts to apply the same standards to high-altitude travel as with commercial flight, the key issue that arises is how to predict which patients will experience a drop in P_aO_2 below the aforementioned thresholds and, therefore, meet criteria for supplemental oxygen. Several prediction tools have been proposed for commercial flight and may also be useful with high-altitude travel. Gong *et al.* demonstrated that a P_aO_2 of 72 mmHg while breathing ambient air at sea level was over 90% successful in predicting P_aO_2 over 55 mmHg at a simulated altitude of 2438 m [121]. However, Christensen et al. reported that 33% of COPD patients with a sea-level P_aO_2 over 72 mmHg experienced a P_aO_2 under 50 mmHg when exposed to the same simulated altitude [117]. Other proposed prediction tools include regression equations that incorporated the patient's FEV_1 as well as baseline P_aO_2 [115], or the hypoxia altitude simulation test [122]. The latter method, which involves inhalation of 15.1% oxygen to simulate the inspired oxygen tension at 2438 m, has been reported to be equivalent to formal hypobaric chamber testing in predicting in-flight hypoxia in both healthy subjects and those with COPD [123].

Beyond the effects on arterial oxygenation, high-altitude exposure may also alter lung mechanics in COPD patients. Several studies have examined the effect of environmental factors in isolation under experimental conditions, but how COPD patients fare in terms of their airflow obstruction at actual high altitude (when all of these factors are working concurrently) is not clear, as no studies have investigated changes in pulmonary function in these patients at terrestrial high altitude. Under simulated high-altitude conditions, the available data are conflicting. The lower air density at high altitude may improve airflow dynamics, although some investigators have shown that hypoxemia and cold air exposure worsen airflow obstruction [124-126]. Finkelstein and colleagues reported an increase in FEV_1/FVC ratio and peak expiratory flow rate (PEFR), and a decrease in vital capacity [127], while Dillard *et al.* found no statistically significant changes in these same variables with COPD patients at a simulated altitude of 2438 m [128].

In COPD patients with bullous emphysema, there is a theoretical concern that bullae may expand and/or rupture during exposure to lower atmospheric pressure. The limited available literature suggests that this concern is not warranted. In a study of nine non-COPD patients rapidly decompressed to a simulated altitude of 13,100 m, bleb/cyst size increased in only one patient, and there were no pneumothoraces [129]. These findings are supported by other studies performed on COPD patients rapidly decompressed to lower atmospheric pressure, which also showed no radiographic or clinical evidence of bullae expansion or pneumothorax [130,131]. A recent survey of complications during commercial flight in 276 women with lymphangioleiomyomatosis – a disorder marked by the presence of extensive cystic lung disease – reported a 2% incidence of pneumothorax among these patients, although the study was unable to determine whether the pneumothoraces may have, in fact, been present to air travel [132].

Secondary PH, a frequent complication in patients with very severe COPD, may predispose to HAPE or worsening RV function during high-altitude travel, as discussed previously. Several studies have shown that long-term high-altitude residents with COPD are at increased risk for cor pulmonale, although data on mortality are conflicting [133,134].

As ventilatory demands increase at high altitude as part of the HVR, it is reasonable to question whether patients with severe COPD can tolerate the increased work of breathing necessary to maintain these increased minute ventilation needs. This issue has not been studied at high altitude, but we may draw tentative conclusions from data involving exercise in COPD patients. Mador *et al.* demonstrated that COPD patients with a mean FEV_1 of 1.79 l raised their minute ventilation to 55.6 l per min during exercise, a value that probably exceeds the ventilatory requirements required at rest at high altitude [135]. Lewis *et al.* compared COPD patients with healthy controls during exercise, finding that COPD patients were able to tolerate the increased work of breathing at the expense of oxygen delivery to other muscle groups [136]. These data suggest that COPD patients should be able to meet resting minute ventilation demands at high altitude, but it remains unknown as to how they will tolerate exercise where, for any given work rate, minute ventilation is higher at high altitude than at sea level [137]. In patients with very severe disease and low maximum voluntary ventilation, minute ventilation during exertion may rise to the level of maximum voluntary ventilation, leading to severe exercise limitation at high altitude.

Based on the information described previously, we propose the following tentative recommendation for high-altitude travel in patients with COPD. Travel to altitudes above 3050 m (10,000 ft) should be avoided, as there are no data concerning COPD patients at such elevations. Individuals already on supplemental oxygen should continue to use it during their high-altitude sojourn, but should increase their flow rate at rest and during exertion. Patients with a FEV_1 under 1.5 l who are not on supplemental oxygen should undergo a pretravel evaluation to determine their need for supplemental oxygen at high altitude, using either the regression equation from Dillard *et al.* or, if available, the high-altitude simulation test [115]. COPD patients in whom the P_aO_2 is predicted to fall below 50 mmHg at the equivalent of 2440 m should consider the use of supplemental oxygen during their sojourn. Because some patients may tolerate the hypoxemia of high altitude without adverse effects, and because arranging oxygen for travel on commercial aircraft can be

difficult and expensive, in some cases it might be reasonable for these patients to travel with a prescription for supplemental oxygen to be filled at their destination, or alternatively monitor pulse oximetry upon arrival and seek help if they have severe hypoxemia or worsening symptoms.

Patients with COPD and PH should be cautioned against travel to high altitude, but if such travel is unavoidable, should use supplemental oxygen and consider nifedipine to prevent HAPE or worsening right heart function, as both therapies have been shown to attenuate HPV in patients with COPD [138, 139]. All patients with COPD should continue their medication regimens when traveling to high altitude, carrying extra short-acting bronchodilators as well as a course of oral steroids to treat any possible exacerbations, particularly if they intend to travel into remote areas away from medical care.

Asthma—Historically, it has been thought that asthmatic patients experience improved symptom control with prolonged stays at high altitude. Higher altitude has been correlated with a lower incidence of exacerbations and nocturnal symptoms, as well as a lower incidence of asthma in children [140,141]. This phenomenon has been attributed in some cases to the reduced allergen burden at higher elevations, as the number of dust mites – allergens inversely correlated with quality of life and FEV_1 in asthmatic patients – is decreased at high altitude, a change associated with a decrease in T-cell and eosinophil activation [2,142-144]. The catecholamine release associated with exposure to high altitude may also contribute to bronchodilation in this environment. While the literature demonstrated the benefit of long-term high-altitude residence for persons with asthma, it is unclear whether these findings can be applied to short-term visitors to high altitude.

Beyond the dust mite issue, other environmental and physiologic factors at high altitude may affect pulmonary function in asthmatic patients at such elevations. The data regarding the effect of hypoxia on airway reactivity are conflicting, as studies report either an increase [145,146], decrease [147] or no change [148,149] in bronchial responsiveness to a methacholine challenge.

With exposure to acute hypoxia, minute ventilation increases, leading to hypocapnea, which in turn may increase airway resistance in asthmatic patients [150,151]. Lower air temperature may also affect individuals with asthma; numerous studies demonstrate that cold air increases airway reactivity in asthmatics more than in healthy control subjects [152-154]. Other literature demonstrates a higher incidence of exercise-induced asthma in cross-country skiers [155-156] and ski mountaineers [157] – athletes who spend large amounts of time exercising and maintaining high minute ventilation rates in cold air, often at high altitude.

While the data noted previously suggest that hypoxia, cold air and hypocapnea may affect airway reactivity in asthmatic patients, it is important to remember that most studies examined the effect of these factors in isolation under experimental conditions. The number of reports involving asthmatics at terrestrial high altitude, where these environmental factors all work simultaneously, is limited. Two studies have reported decreased bronchial reactivity to hypotonic aerosol in patients with mild, well-controlled asthma after ascent to 4559 and

5050 m [158,159], while another study demonstrated a decrease in PEFR during a trek to Everest Base Camp [160]. However, the utility of the data from the latter study is limited, as many subjects also received acetazolamide or dexamethasone, which may have altered airway reactivity.

Based on the available data, we recommend the following regarding asthmatic patients traveling to high altitude. Individuals with mild intermittent or mild persistent asthma should be able to ascend safely to 5000 m. They may do well at even higher elevations, but there is currently no literature to support firm conclusions in this regard, aside from a recent report of asthmatic patients who successfully summited Mount Kilimanjaro [161]. Asthmatic patients with severe disease, or those experiencing or recovering from an asthma exacerbation, should avoid travel to high altitude, particularly into remote areas away from medical care. Patients should continue their medication regimens and should bring a supply of rescue inhalers and oral steroids. Those individuals with a strong exercise component to their symptoms who intend to engage in a high level of physical activity at high altitude should use short-acting bronchodilators prior to activity, and may consider adding a leukotriene-receptor blocker or cromolyn sodium. The latter medication may also protect against cold-mediated bronchoconstriction [162]. In addition, patients should consider using a scarf, face mask or balaclava to warm and humidify inhaled air in particularly cold, dry environments. If patients wish to monitor their symptoms objectively, they should use a fixed-orifice peak flow meter, as variable orifice meters may not function well at high altitude [163].

Cystic fibrosis—Cystic fibrosis (CF) is an autosomal recessive disorder marked by defective chloride ion transport affecting multiple organ systems, in which most morbidity and mortality occurs due to pulmonary complications. Only a few studies have been conducted in this population at simulated or actual high altitude. The available data suggest that many CF patients experience significant hypoxemia at rest and with mild exercise, but do not develop significant clinical symptoms of hypoxemia in hypobaric hypoxic conditions [164-166]. Studying adult CF patients with a wide range of FEV_1 values at an altitude of 2650 m for several hours, Fischer *et al*. found that P_aO_2 dropped below 50 mmHg in a third of the subjects at rest, and over two-thirds of the subjects with mild exercise [165]. These authors also reported a strong correlation between the degree of baseline obstruction and the severity of altitude-related desaturation, and demonstrated improvements in FEV_1 and PEFR at high altitude [165].

As with literature on COPD patients, the studies on CF patients are limited by the short duration of hypoxic exposure. As a result, it remains unclear how these patients will fare with exposures lasting days or weeks. Speechly-Dick *et al.* described two cases of CF patients who developed severe PH and acute right heart failure while on high-altitude trips [167], suggesting that complications may occur with long sojourns in certain patients.

For CF patients who wish to travel to high altitude, pretravel spirometry is recommended to predict which patients will likely have significant desaturation during their sojourn [165]. Buchdahl *et al.* validated spirometry as a better predictor of altitude-induced desaturation in CF patients (7-19 years of age) when compared with the hypoxia altitude stimulation test

[168]. Patients predicted to have a P_aO_2 less than 50 mmHg should travel with either supplemental oxygen or a prescription that can be filled at their destination if they experience severe hypoxemia or worsening symptoms. During high-altitude travel, CF patients should maintain their baseline therapeutic regimens, including inhalers/nebulizers, chest physiotherapy, mucolytics and prophylactic antibiotics.

Restrict lung disease

Interstitial lung disease—Only a few studies have addressed the effect of high-altitude travel on patients with interstitital lung disease (ILD). Seccombe *et al.* exposed a mixed group of ILD patients to normobaric hypoxia (F_iO_2:0.15), demonstrating increased dyspnea and a decrease in P_aO_2 both at rest and with exercise [118]. These findings were in agreement with those of Christensen *et al.*, who found that P_aO_2 decreased from a mean of 78 ± 12 mmHg at sea level to 49 ± 8 mmHg at rest, and 38 ± 7 mmHg with mild exercise at a simulated altitude of 2438 m [169]. They also demonstrated that supplemental oxygen at a rate of 2 l per min at rest and 4 l per min with exercise was sufficient to keep the P_aO_2 above 50 mmHg in these patients [169].

No studies have examined changes in pulmonary hemodynamics of mechanics in ILD patients at simulated or actual high altitude. It is known, however, that many of these patients develop PH as a complication of their disease, which – as noted earlier – predispose them to HAPE or RV dysfunction at high altitude.

Individuals with ILD should be evaluated at sea level with pulmonary function tests and arterial blood gas analysis before commercial flight or other high-altitude travel to determine any need for supplemental oxygen. If the high-altitude simulation test is not feasible, the regression equation provided by Christensen *et al.* [169] is one of the few available tools for predicting the patient's P_aO_2, although it explained only 77% of the variance in P_aO_2 at 2438 m in their study and has not been validated, since:

$$P_aO_{2(\text{predicted})} = 0.74 + (0.39 \times P_aO_2SL) + (0.033 \times \text{TLC})$$

(where P_aO_2SL = P_aO_2 while breathing ambient air at sea level; and TLC = percent of predicted total lung capacity).

If PH is suspected in an ILD patient, echocardiography should be performed prior to high-altitude travel. Those patients found to have PH should be managed according to the guidelines provided earlier.

Chest wall abnormalities—Kyphoscoliosis and other chest wall disorders that cause a restrictive ventilator pattern may be associated with pulmonary complications that predispose to problems at high altitude – these may include central sleep apnea, alveolar hypoventilation, PH, cor pulmonale and right-to-left shunt [170,171]. For example, Noble *et al*. described the onset of PH and acute right heart failure in a previously stable patient with kyphoscoliosis during an intercontinental flight [172]. Several studies have also documented the development of severe hypoxemia in these individuals when exposed to hypoxic

conditions equivalent to those experienced on aircraft [169,173]. Prior to high-altitude travel, patients with moderate to severe kyphoscoliosis should undergo pulmonary function testing and possibly echocardiography to rule out PH. Patients found to have PH should be managed according to the guidelines described previously.

Ventilatory disorders

Obstructive sleep apnea—In the only study of OSA patients in hypoxic conditions, Burgess *et al.* performed overnight polysomnography on five individuals with moderate OSA, demonstrating that the respiratory disturbance index (RDI) for obstructive events decreased from 25.5 ± 14/h at sea level to 0.5 ± 0.7/h at a simulated altitude of 2750 m [174]. The reason for this finding is unclear, but it is probably not due to the effects of hypobaria on upper airway airflow dynamics, as the study was conducted under normobaric conditions. The marked decrease in the obstructive RDI was accompanied by a substantial increase in the RDI for central events, but it is not clear whether the latter finding featured the same degree of daytime cognitive impairment and wakefulness as the patient's sea-level OSA. As this was a small study, our ability to draw firm conclusions is limited, and as sleep apnea appears to persist in one form or another at high altitude in these patients, it would be reasonable to continue positive airway pressure therapy at high altitude, provided the patient has adequate access to power sources and can travel with their continuous positive airway pressure (CPAP) machine.

Obesity hypoventilation syndrome—Many patients with obesity hypoventilation syndrome (OHS) develop PH and cor pulmonale [175,176], which may make them more susceptible to HAPE and/or acute right heart failure when they travel to high altitude, developing further alveolar hypoxia and increased PAP. This phenomenon has been reported in a morbidly obese individual during commercial air travel [177]. OHS patients may also be at higher risk for AMS, as both obesity and nocturnal hypoxemia have been identified as risk factors for AMS [36,178,179].

Even if patients with OHS avoid the acute complications of high-altitude travel, they may be at risk for problems with more prolonged exposure, as there is a high prevalence of PH in obese persons living at moderately high altitudes (2100-2400 m) [180].

Considering the risks of AMS, PH, HAPE and possibly decompensated right heart failure, patients with OHS should avoid high-altitude travel without supplemental oxygen. They should continue their baseline treatment regimens, including CPAP or respiratory stimulants such as progesterone [181,182]. Morbidly obese patients should avoid acetazolamide, as this may paradoxically worsen pre-existing hypercapnea in individuals who cannot mount an adequate ventilatory response to an acetazolamide-induced metabolic acidosis.

Neuromuscular disorders—Several disorders that affect the central or peripheral nervous system may significantly impair ventilation, putting patients at increased risk for problems at high altitude. For example, patients with muscular dystrophy or amyotrophic lateral sclerosis often have chronic alveolar hypoventilation and may not be able to adequately increase their minute ventilation in response to the hypoxia of high altitude. Patients with Parkinson's disease [183] and myotonic dystrophy [184] may have a blunted

HVR that can predispose them to more severe hypoxemia at high altitude. Persons with myotonic dystrophy [185] and Duchenne muscular dystrophy [186,187] often develop sleep-disordered breathing, which could lead to profound nocturnal hypoxemia during sleep at high altitudes. Finally, patients with bilateral diaphragmatic paralysis may develop hypoventilation and hypoxemia while supine at sea level [188, 189] and, therefore, may also be at risk for significant nocturnal hypoxemia during high-altitude travel.

Patients with these disorders should undergo pretravel evaluation to rule out the existence of complications that may predispose to illness at high altitude. Those with underlying sleep apnea should consider traveling with CPAP therapy, while patients with baseline hypoventilation should probably avoid high-altitude travel altogether. If such travel is necessary, supplemental oxygen should be strongly considered, as should nocturnal bi-level positive airway pressure. Patients with significant nocturnal desaturation at sea level should sleep with supplemental oxygen at high altitude. Supplemental oxygen should be used carefully in these patients, as excessive oxygen administration may worsen underlying hypercapnea [190]. Patients with bilateral diaphragmatic paralysis should consider either nocturnal oxygen therapy or nocturnal bilevel positive airway pressure.

Abnormal ventilatory drive—The HVR plays a crucial role in acclimatization to high altitude; blunted HVR may be a risk factor for both AMS [44,191] and HAPE [18-20]. As HVR is largely mediated by the carotid body chemoreceptors, patients with damaged or absent carotid bodies may be at risk for impaired ventilatory responses and significant hypoxemia at high altitude. One group of patients at risk for this phenomenon includes those who have undergone unilateral or bilateral carotid endarterectomy (CEA) as impaired HVR has been documented in this population [192,193]. Roeggla *et al.*, for example, examined the effect of moderate altitude (1600 m) on gas exchange in patients before and after unilateral CEA and found that, following surgery, patients developed worse hypoxemia and less hyperventilation when compared with their presurgery baseline [194]. Such problems may not be limited to post-CEA patients. Basnyat described a patient who developed HACE at an altitude of 3600 m, 8 years after having surgical resection of bilateral carotid body tumors [195]. Other case reports have implicated a history of neck irradiation and subsequent carotid injury in the development of AMS [196], HACE and HAPE [197].

Patients who have had bilateral carotid surgery should undergo a pretravel evaluation to determine whether they can mount adequate ventilatory responses and maintain oxygenation under the conditions of high altitude. Those who become very hypoxemic during evaluation should avoid travel to high altitude without supplemental oxygen. Unlike with COPD and restrictive lung diseases, there are currently no predictive methods available to determine the degree to which such patients may become hypoxemic at high altitudes. In the absence of such tools, a prudent approach would be to perform a high-altitude simulation test and consider initiating supplemental oxygen therapy during high-altitude travel in those patients in whom the P_aO_2 falls below 50 mmHg. Possible prophylactic approaches for these patients may include the use of central respiratory stimulants – such as acetazolamide, progesterone or theophylline – although their use has not been studied at high altitude in these patients. These agents increase minute ventilation by mechanisms independent of the carotid bodies,

and have been shown to improve central sleep apnea [198], nocturnal hypoxemia [88] and periodic breathing at high altitude [62].

Expert commentary

In this review, we have discussed pulmonary complications that can develop with both acute and chronic high-altitude exposure, and we have considered whether and how patients with various forms of underlying lung disease can tolerate exposure to this environment. The underlying pathophysiology and appropriate means for preventing and managing the acute and chronic forms of high-altitude illness have been well established, and there is a considerable body of evidence available to guide current practices with regard to these illnesses. The situation is markedly different, however, with regard to the safety of high-altitude travel in patients with underlying lung disease, as few systematic studies have been conducted with these patient populations at terrestrial high altitude. In the absence of such studies, the risks and likely outcomes of high-altitude travel in these patients must be assessed based on a review of the few available studies and case series/reports, as well as an understanding of the manner in which the underlying pathophysiology of the patient's disease may interact with the hypoxic environment at high altitude. A careful pretravel assessment should be performed for all patients with moderate-to-severe underlying lung diseases who wish to travel to high altitudes, and patients should travel with plans for monitoring symptoms and managing their disease during their sojourn.

Five-year view

Further investigations continue into the underlying pathophysiology of HAPE and other forms of acute altitude illness. Additional studies may shed light on the mechanism by which dexamethasone plays a role in HAPE prevention, while other work may clarify whether acetazolamide, long used to prevent AMS and decrease central sleep apnea at high altitude, can play a role in HAPE prevention and treatment due to its effects on HPV.

Regarding the safety of travel to high altitudes with underlying lung disease, considerably more data are needed to clarify the risks of high-altitude travel in these individuals and establish proper management strategies, but the pace and volume of this work is likely to be limited compared with the research examining the acute altitude illnesses. Given the large numbers of people traveling to high altitudes for work or pleasure and the incidence of certain medical conditions in the general population, it is likely that many high-altitude sojourners have underlying medical diseases. Further studies examining patients with lung disease and other common forms of chronic illness would be of great assistance to clinicians who provide pretravel advice to these patients. One possible direction of future research is the validation of a pretravel assessment to more accurately predict the risk of high-altitude travel in patients with a given form of lung disease.

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Table 1
Pharmacologic and Non-Pharmacologic Measures to Prevent HAPE

Method/Agent	Dose/Description	Adverse Effects
Gradual Ascent	Limit increase in the sleeping elevation to < 500 meters/day when above 2500 meters altitude	None
Nifedipine	30 mg extended release orally twice daily	Reflex tachycardia, peripheral edema, rare hypotension
Salmeterol *	125 μg inhaled twice daily	Tachycardia, agitation
Tadalafil	10 mg orally twice daily	Headache, dyspepsia
Dexamethasone	8 mg orally twice daily	Mood disturbances, hyperglycemia,possible rebound effect when discontinued

* Should not be used as monotherapy

Table 2
Strategies Used in the Treatment of HAPE

Method/Agent	Dose/Description	Adverse Effects
Immediate Descent	Descend 1000 or more meters or until symptoms resolve	None
Supplemental Oxygen	Deliver oxygen by nasal cannula or face mask at flow rates sufficient to raise $S_aO_2 > 90\%$	None
Rest	Limit strenuous activity, particularly during descent (eg. travel without a pack, evacuation by vehicle or animal)	None
Portable Hyperbaric Chamber	2-4 psi for several hours, depending on chamber model; should not delay descent in situations where descent is feasible	Return of symptoms after removal from chamber; Claustrophobia
Nifedipine	30 mg oral extended release twice daily	Tachycardia, peripheral edema, hypotension