Physiology in Medicine: Acute altitude exposure in patients with pulmonary and cardiovascular disease

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TRAVEL HAS BECOME MORE AFFORDABLE, with a dramatic increase in the number of commercial air passengers. Improved high-altitude airports, railways, and roads allow rapid access to altitude destinations for recreational and occupational reasons without acclimatization. Many patients with chronic cardiac and pulmonary illnesses now survive longer, and the emphasis on rehabilitation/physical activity, rather than rest, may reduce the perception of limits of what travel can be undertaken. Importantly because altitude and air travel are generally well tolerated, there are few adverse events that would generate any perception of risk in the general public.

The physiology of moderate and high altitude has been extensively described in healthy individuals (70, 73). In contrast, there is a paucity of data pertaining to those who have reduced reserve due to pulmonary and/or cardiac disease. Information regarding the risk of adverse events during short-duration commercial flight may not reflect the risk of longer flights or travel to altitude. Although adverse events are infrequent (18, 54), there should be limits—not only for safety but also in circumstances where a traveler ascends to an altitude at which they are so limited by breathlessness they cannot enjoy the experience.

This Physiology in Medicine article aims to integrate knowledge in relation to exercise and altitude physiology to provide a structure in which the risks of travel can be considered. Importantly, each patient and travel context should be regarded as individual, and we cannot and do not seek to establish single safety thresholds that can be applied to all.

HYPOBARIC AND HYPOXIC ENVIRONMENTS

All terrestrial travel occurs within the atmospheric layer of the troposphere where the composition of gases is constant. During ascent to altitude, barometric pressure (P_B) declines exponentially, and in keeping with Dalton’s law, the partial pressure of oxygen falls accordingly. P_B directly determines the pressure of inspired oxygen within the airways (P_{O_2}^{in}) = 0.2094 (P_B - 47) (73) and hence the possible alveolar oxygen pressure. Arterial hypoxemia is an inevitable consequence. High altitude typically refers to elevations over 2,000 m (6,560 ft), but no single value is an adequate definition for all patients. The characteristics of a selection of travel destinations and the fraction of inspired oxygen (F_{O_2}) at sea level that would approximate the ambient P_{O_2} at these destinations are shown in Table 1.

For the great majority of travelers, the lowest atmospheric pressure conditions that they are likely to experience will be during a commercial aircraft flight. Regulations require cabin pressure to be no less than P_B equivalent to an altitude of 2,438 m (8,000 ft, P_B 574 mmHg)(17). Short-haul flights commonly have mean cabin pressures close to this minimum (19), whereas pressures are commonly higher in long-haul wide-body aircraft. A mean cabin pressure altitude of 1,600 m (5,250 ft) has been reported in Boeing 747 flights averaging 10 h in duration (40), similar to Denver, Colorado. The minimum standard can be simulated in a hypobaric chamber or by breathing a low-oxygen gas mix with F_{O_2} of 0.154 [altitude simulation test (AST)(28)]. The pressure of arterial oxygen (P_{aO_2}) during an AST correlates well with oxygenation measured during longer equivalent P_B exposure within a hypobaric chamber (49, 51), during commercial flight (41, 42), and at terrestrial altitude (44) in normal subjects and in patients with lung disease. Therefore it appears that normo- and hypobaric hypoxia have similar effects on arterial oxygenation in the context of short-term travel such as aircraft flight or day trip to altitude.
THE NORMAL PHYSIOLOGICAL RESPONSE TO ACUTE ALTITUDE EXPOSURE

The primary physiological compensation for an acute decrease in \( P_{\text{aO}_2} \) is to increase alveolar ventilation. Although highly variable, this is typically seen when \( P_{\text{aO}_2} \) falls to 50–60 mmHg, equivalent to an altitude of \( \sim 3,000 \) m (9,840 ft, \( P_{\text{aO}_2} \) 100 mmHg) (55). At this level of hypoxemia with adequate circulation, the impact is minimal because the oxygen gradient between systemic capillaries and sites of oxygen utilization is sufficient. Further falls in \( P_{\text{aO}_2} \) result in ventilation increasing hyperbolically, via increases in tidal volume and respiratory rate, with a reduced pressure of arterial carbon dioxide and alkalemia. Acute hypocapnia is the hallmark of a hypoxic ventilatory response. In acute exposure, before acclimatization has occurred, the resulting leftward shift in the oxyhemoglobin dissociation curve improves diffusive oxygen uptake, because arterial oxygen content will be higher for any given \( \text{PaO}_2 \) (73).

Hyperventilation thus is critically important in the mitigation of hypoxemia—an adaptive mechanism that is compromised if the increase in minute ventilation is limited in the presence of lung disease. With acute exposure to altitude, there is an increase in sympathetic activity and a concurrent decrease in parasympathetic activity (37). Cardiac output increases primarily through increased heart rate (68). Vasodilatation reduces systemic vascular resistance, and therefore systemic blood pressure changes only minimally to altitudes \( \sim 4,600 \) m (68, 73). Simulation studies suggest that ventricular contractile function is maintained even up to the summit of Mt. Everest (8,800 m, 29,000 ft) (66). Increased cardiac output is required to mitigate the reduction in tissue oxygen delivery in the presence of hypoxemia. It follows that the presence of cardiac disease may severely compromise this adaptive increase in cardiac output. At low altitude, hypoxic pulmonary vasoconstriction (HPV) is a highly variable response that mediates ventilation-perfusion matching by diverting blood flow from hypoxic to non-hypoxic lung units. In response to a lower pressure of alveolar oxygen at altitude, the pulmonary vasculature constricts and pulmonary vascular resistance increases. Pulmonary artery pressure is therefore elevated, comparatively higher for any level of cardiac output than at sea level (30). Although heart rate does not change significantly when healthy travelers are inactive during commercial flight (41), a mean 10% increase in pulmonary artery pressure has been recorded during an AST (35). This process may become acutely important in those with pre-existing elevated pulmonary arterial pressures. Patients with pulmonary hypertension (Grade II–III heart failure) have been shown to experience larger (13%) and more variable increases in pulmonary artery pressures during an AST than healthy normals (35).

Mild hypoxemia at mild-moderate altitude becomes more pronounced with exercise and increasing altitude (69, 70). With a lower \( P_{\text{aO}_2} \), there is a reduced oxygen driving pressure across the blood-gas barrier. The corresponding elevated cardiac output decreases pulmonary transit time and compromises equilibration of oxygen (62). This results in a diffusion limitation of oxygen that increases with altitude. At moderate altitudes similar to many ski fields (2,500 m), oxygen saturation measured by pulse oximetry (\( \text{SpO}_2 \)) is normally \( \sim 92\% \) at rest (\( P_{\text{aO}_2} \) \( \sim 60 \) mmHg) (45, 56). Values are similar in healthy normal travelers of varying ages during commercial flight (41, 51), during an AST (41), and within a hypobaric chamber simulating 2,438 m (49, 51). At this altitude, maximal oxygen uptake is 90–95% of sea level values (12) and falls exponentially with increasing elevation.

In summary, during ascent to altitude barometric pressure, pressure of inspired oxygen and arterial oxygenation fall exponentially. Normal subjects respond to acute altitude exposure via well-defined physiological processes affecting ventilation and circulation. Serious clinical consequences are rare during commercial aircraft flight or ascent to the equivalent altitude of \( \sim 2,438 \) m (8,000 ft). At mostly higher altitudes, however, there are acute mountain illness syndromes that befall normal subjects, and these are briefly discussed below.

Acute Mountain Illness

The most common medical concern for unacclimatized healthy travelers to areas above \( \sim 2,000 \) m (6,560 ft) is the possible development of acute mountain illnesses. Incidence is more common with rapid ascent, higher altitude reached, younger age, and individual physiology as reflected in previous episodes (32). There are three well-described altitude illnesses.

1) Acute mountain sickness (AMS) is defined as headache and at least one other symptom that includes gastrointestinal symptoms (anorexia, nausea, or vomiting), insomnia, dizziness, and lassitude or fatigue. AMS is attributable to hypoxemia and alkalosis. A high incidence (16–80%) has been identified at altitudes between 2,500 and 3,740 m (50, 56, 60), but symptoms generally subside within 2–3 days at the same altitude, although insomnia may persist beyond that time (72).
AMS as a sole effect of travel to altitude may carry little intrinsic risk.

2) High-altitude cerebral edema (HACE) is rare. Typically there are preceding symptoms of AMS, and this may represent the severe end of an illness continuum. It is likely that a combination of hemodynamic factors, including sustained vasodilatation, impaired cerebral autorregulation, and elevated cerebral capillary pressure, are responsible for the formation of vasogenic edema (32). If not rapidly addressed, ideally by descent, this illness is potentially fatal.

3) High-altitude pulmonary edema (HAPE), also potentially fatal, is associated with increased pulmonary arterial pressures related to HPV. It is postulated that uneven HPV elevates pressure in pulmonary capillaries, leading to stress failure (38). The factors that have been associated with an increased genetic susceptibility include a strong HPV response, abnormal increase in pulmonary artery pressure, and a reduced hypoxic ventilatory response (22, 31, 33). Supplementary oxygen will significantly reduce pulmonary artery pressure and is the primary treatment for HAPE.

It is reasonable to assume that patients with pre-existing hypoxemia and/or vascular disease may be more susceptible to HAPE and HACE, but this has not been directly studied. A risk threshold for pulmonary arterial pressure and incidence of HACE has not been identified (47). In older travelers to 2,500 m, there was no greater incidence of AMS in those that had pre-existing pulmonary or cardiac disease (56). However, those with pre-existing lung disease were shown to have increased incidence of AMS from a large cohort of tourists to 1,900–2,900 m (36). The risk of AMS is consistently increased with obesity, and alcohol use increases the risk of upper gastrointestinal bleeding (75).

For susceptible healthy travelers, prophylaxis with acetazolamide and vasodilators that inhibit HPV (e.g., nifedipine, sildenafil) may be an option (32, 46). Common wisdom dictates that any history of a severe altitude-related illness should be considered a contraindication for repeat travel to similar altitudes in patients with chronic disease.

In summary, severe forms of these classical altitude illnesses are rarely, if ever, observed during commercial flight or gradual ascent to equivalent altitudes. With rapid ascent and to higher altitudes they become more frequent. More needs to be known about the prevalence and severity of these syndromes in patients with moderate or severe cardiovascular and pulmonary disease.

THE RESPONSE TO ACUTE ALTITUDE EXPOSURE IN PATIENTS WITH CHRONIC DISEASE

In any individual, oxygen uptake and utilization requires adequate ventilation, pulmonary gas transfer, effective circulation, oxygen carriage, peripheral oxygen extraction, and sufficient muscle strength relative to load. Symptoms including breathlessness will limit activity when capacity at any of these stages is exceeded at a given workload.

For those with reduced physiological reserve planning travel to altitude or by commercial aircraft, any of these responses may be compromised. The most important potential physiological limitations experienced by patients with pulmonary and cardiac disease are presented in Table 2.

Pulmonary Disease

At equivalent altitude, greater hypoxemia is consistently seen in patients with pulmonary disease, including chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), cystic fibrosis, and kyphoscoliosis, than in healthy subjects. Most data relate to commercial aircraft flight or similar short-term altitude exposure.

Patients with moderate COPD (sea level $P_{A\text{O}_2}$ 75 mmHg) were studied during a day trip to 2,086 m (Mt. Hutt Ski Field, New Zealand) and were found to have a resting $P_{A\text{O}_2}$ $\approx$50 mmHg (44). This finding is consistent with studies of COPD or pulmonary restriction patients with near normal $P_{A\text{O}_2}$ at sea level $\approx$80 mmHg who achieve a $P_{A\text{O}_2}$ $\approx$50 mmHg both during an AST and seated in flight (13, 14, 42, 43, 51, 63).

It is important to note that sea level oxygenation and lung function correlate poorly with oxygenation at altitude in patients with pulmonary disease (Fig. 1). Thus medical guidelines were recently amended and no longer include resting sea level $P_{A\text{O}_2}$, $S\text{pO}_2$, or lung function as an indication of in-flight oxygenation or risk of complications (3). Intriguingly, altitude

Table 2. Examples of physiological limitation to altitude in patients with pulmonary and cardiac disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Physiological Consequence of Altitude Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>Hypoxic ventilatory response *Inability to adequately increase $V_{E}$ *Increased work of breathing</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>Gas expansion</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>Hypoxic pulmonary vasoconstriction *Risk of barotrauma with rapid ascent if bronchogenic cyst present</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>Sympathetically mediated circulatory demand *Lower work threshold for the onset of symptoms; angina/arrhythmia/schemia</td>
</tr>
<tr>
<td>Heart failure and valvular disease</td>
<td>Sympathetically mediated circulatory demand *Inability to adequately increase cardiac output</td>
</tr>
<tr>
<td></td>
<td>Hypoxic ventilatory response *Inefficient ventilation ($V_{E}/V_{CO_2}$) *Increased work of breathing</td>
</tr>
</tbody>
</table>

$V_{E}$, minute ventilation; $V_{CO_2}$, carbon dioxide production.
and altitude simulation are well tolerated at levels of oxygenation that would cause concern in the context of acute medical illness, where the mechanisms causing hypoxemia are very different. It is likely that these patients have some reserve in peripheral oxygen extraction, with further reductions in mixed venous oxygen saturation preserving oxygen uptake in the face of lower arterial oxygen saturation (74). Cardiac output may also be further increased.

Adequate hyperventilation at rest or during exercise at altitude is problematic for patients with either obstructive or restrictive pulmonary disease. In COPD, dynamic hyperinflation may occur at altitude as it does during exercise at sea level. This would create mechanical disadvantage further increasing the work of breathing. Specific data confirming this are required. In ILD there is reduced lung compliance caused by increased elastic loading that similarly increases the work of breathing. Typically minute ventilation is increased through increased respiratory rate rather than tidal volume. To the extent that this pattern of ventilation reduces mechanical work, it increases dead space ventilation (39). Whenever a greater percentage of oxygen uptake is required for an increased work of breathing, there is a “steal” of cardiac output that might otherwise service locomotor work. The combination of respiratory muscle fatigue and reduced blood flow to locomotor muscles contributes to impairment of exercise performance (23).

Although the level of resting hypoxemia at moderate altitude generally elicits minimal symptoms in subjects with pulmonary disease, physiological impairment becomes evident once a mild exercise task is attempted. \( P_{aO_2} \) with exercise during an AST (replicating walking the aircraft cabin aisle) often falls to \( \approx 40 \) mmHg both in patients with COPD (13, 51, 63) and in patients with restrictive disease (14, 63). Similarly on Mt. Hutt (2,086 m), subjects with COPD had difficulty completing a 6-min walking task because of dyspnea, with a mean \( P_{aO_2} \) of 41 mmHg, tachycardia to 130 beats/min, and an elevated arterial carbon dioxide tension (compared with rest) suggesting true ventilatory limitation (44). Younger subjects with cystic fibrosis at a terrestrial altitude of 2,650 m also desaturate significantly after exercise (\( P_{aO_2} < 50 \) mmHg) (27). Of relevance, flight surveys suggest that patients with similar disease severity are often traveling without supplemental oxygen (18, 54). The low frequency of reported adverse events suggests that this degree of hypoxemia can be tolerated for short periods. Typically minimal physical exertion is undertaken during commercial air travel.

According to Boyles Law, during ascent any trapped, non-communicating gas will expand. Barotrauma is generally not a concern during terrestrial travel, apart from some mountain cable cars, as the rate of change in air pressure is slow. As cabin pressure decreases to cruising altitude, noncommunicating gas will expand by \( \approx 33\% \) within minutes. Free expansion without rupture of a very large pulmonary cyst could compromise ventilation to adjacent lung units, but the greatest risk is cyst rupture. This has been reported in individuals with non-communicating bronchogenic cysts and bulla greater than 500 ml. In these cases, gas expansion during decompression ascent in commercial aircraft caused a rupture of the cyst wall, systemic gas embolism, and brain injury (7, 16, 52, 78).

However, patients with generalized bullous emphysema are usually at low risk of cyst rupture, because intra- and interlobar collateral ventilation allows even relatively poorly ventilated lung units to decompress (15). Reported cases of safe air travel in individuals with large thick-walled cysts or a chronic pneumothorax suggest that these cavities can withstand an increase in pressure relative to that in adjacent lung (20).

Although decompression studies within a hypobaric chamber have shown no significant distension or pneumothoraces in patients with bullae, blebs, or pulmonary cysts (53, 67), catastrophic in-flight case reports as described above merit conservative clinical recommendations. A recent description of mortality after an exacerbation of a pre-existing pneumomediastinum in-flight demonstrates the unpredictability of adverse events (77).

Travel to altitude for people living with asthma is generally safe (75). For those with stable but fixed airflow limitation, the considerations are similar to those for COPD. Exercise in cold air at altitude enhances airway dehydration and the propensity to develop exercise-induced bronchoconstriction. This can be minimized by achieving optimal asthma control before travel and use of short acting beta-agonists pre-exercise. Generally, pressurized metered-dosed inhalers work effectively at moderate altitude. Note there may be a reduced total number of doses per pressurized canister (57). Unstable asthma is seen as a contraindication to travel because of the risk of a severe exacerbation. Management is further compromised in remote regions.

**In summary, the additional stresses on patients with pulmonary disease exposed to altitude or commercial aircraft travel are:**

1. **Limited ability to mount a ventilatory response to hypoxia, resulting in worsening hypoxemia and failure to reduce arterial pressure of carbon dioxide.**
2. **Higher pulmonary artery pressures in response to hypoxia, increasing right ventricular afterload.**
3. **Risk of rupture of pulmonary bullae when ascent is rapid.**
4. **A reduction in already limited exercise capacity.**

**Cardiac and Vascular Disease**

A consistent finding across a range of cardiac disorders is that symptom-limited exercise performance declines at altitude.
as it does in normal subjects. The extent to which this becomes a problem during travel is dependent on the severity of cardiac disease and the altitude. Increased right ventricular afterload related to HPV and increased left ventricular afterload from increases in circulating catecholamines may contribute to this. The magnitude of these effects relative to that of simple reduction in myocardial oxygen delivery at altitude cannot be determined.

In patients with stable, known coronary artery disease (CAD), coronary vasodilatation does not occur during severe hypoxia as it does in healthy subjects (5, 76). Such patients do have a reduction in symptom-limited exercise capacity at altitude but without serious cardiac events between 2,500 and 4,200 m (21, 25, 61). Patients with severe CAD or recent acute myocardial infarction (AMI) have not been systematically studied, with the exception of those who had undergone coronary revascularization. In these subjects, exercise at 3,400 m did not elicit any adverse events after 6 mo of rehabilitation (61).

Addressing this question in a different way, epidemiological studies of hikers and skiers conducted at altitudes between 1,000 and 5,000 m, show a very low risk of acute coronary events such as AMI and sudden cardiac death (11, 29, 64). These cohorts are likely to include significant numbers with diagnosed or undiagnosed cardiac disease. In an Austrian survey of alpine skiers and hikers, 11–13% had known cardiac disease (26). Sudden cardiac death is the most frequent cause of nontraumatic death in men aged over 34 yr during leisure activities at altitude such as hiking and downhill skiing. Previous AMI, known CAD without prior AMI, and hypertension have been identified as independent risk factors (10). There is no evidence that these risks are higher at altitude than they would have been at sea level in similar subjects.

Those with pre-existing pulmonary hypertension will experience further elevation in pressures at altitude due to HPV. This causes increased pulmonary vascular resistance, particularly during exercise (30). During an AST (9) and in-flight (59), patients with pulmonary hypertension demonstrate arterial hypoxemia (PaO₂ ∼60 mmHg) similar to that in normal subjects that is not predictable from disease severity (9). The data in these studies did not include measures of right heart function, which are necessary to assess the load on, and any risk to, the right ventricle.

In an observational study of patients with pulmonary hypertension, no serious adverse events were seen in commercial aircraft flights averaging 3.5 h, but some subjects did use supplemental oxygen (59). Hypoxemia was noted to worsen during walking in the aircraft. Patients with chronic heart failure (Grade I-III) (35) and cyanotic congenital heart disease (34) also have near-normal oxygenation during an AST. At simulated 3,000 m, maximal exercise in patients with Grade

Table 3. Summary of the current guidelines for patients with pulmonary and cardiac disease planning travel on commercial aircraft

<table>
<thead>
<tr>
<th>Pulmonary Disease</th>
<th>Investigation</th>
<th>Recommendations</th>
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<tbody>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>PaO₂&lt;50mmHg during AST</td>
<td>Supplemental O₂</td>
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<tr>
<td></td>
<td>SpO₂≥85% during AST</td>
<td>1,2,3</td>
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<tr>
<td>Interstitial lung disease</td>
<td>PaO₂&lt;50mmHg during AST SpO₂≥85% during AST</td>
<td>Supplemental O₂</td>
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<tr>
<td></td>
<td></td>
<td>1,2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Kyphoscoliosis and neuromuscular disorders</td>
<td>All require an AST</td>
<td>Emergency supply of antibiotics</td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
<td>1</td>
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<tr>
<td>Pneumothorax</td>
<td>Closed</td>
<td>Individual clinical assessment</td>
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<tr>
<td></td>
<td>Traumatic</td>
<td>Unrestricted travel</td>
</tr>
<tr>
<td></td>
<td>With comorbidity without pleurodesis</td>
<td>Contraindication to travel</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>SpO₂&lt;90% during AST</td>
<td>Travel 2 wk following resolution</td>
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<tr>
<td></td>
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<td>1,4</td>
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<table>
<thead>
<tr>
<th>Cardiac and vascular disease</th>
<th>Functional class (New York Heart Association Grading)</th>
<th>Recommendations</th>
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<tbody>
<tr>
<td>Pulmonary hypertension</td>
<td>I-II</td>
<td>Unrestricted travel</td>
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<tr>
<td></td>
<td>III-IV</td>
<td>Supplemental O₂</td>
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<tr>
<td>Angina pectoris</td>
<td>I-II</td>
<td>Unrestricted travel</td>
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<td></td>
<td>III-IV</td>
<td>Supplemental O₂</td>
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<tr>
<td></td>
<td>IV</td>
<td>Avoid travel unless essential or</td>
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<tr>
<td></td>
<td></td>
<td>supplemental O₂ and accompanied</td>
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<td>6-8 wk recovery prior to elective</td>
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<tr>
<td>Post myocardial infarction</td>
<td>I-II</td>
<td>Unrestricted travel</td>
</tr>
<tr>
<td></td>
<td>III-IV</td>
<td>Supplemental O₂</td>
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<td></td>
<td>IV</td>
<td>Avoid travel unless essential or</td>
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<td></td>
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<td>supplemental O₂ and accompanied</td>
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<tr>
<td>Heart failure</td>
<td>I-II</td>
<td>Unrestricted travel</td>
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<td></td>
<td>III-IV</td>
<td>Supplemental O₂</td>
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<td>Avoid travel unless essential or</td>
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<td>supplemental O₂ and accompanied</td>
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<tr>
<td>Cyanotic congenital heart disease</td>
<td>I-II</td>
<td>Supplemental O₂</td>
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<td></td>
<td>III-IV</td>
<td>Supplemental O₂</td>
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<td>Avoid travel unless essential or</td>
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<td>supplemental O₂ and accompanied</td>
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<tr>
<td>Valvular disease</td>
<td>I-II</td>
<td>Unrestricted travel</td>
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<td></td>
<td>III-IV</td>
<td>Supplemental O₂</td>
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<tr>
<td></td>
<td>IV</td>
<td>Supplemental O₂</td>
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<tr>
<td>Stable arrhythmia</td>
<td>I-II</td>
<td>Unrestricted travel</td>
</tr>
<tr>
<td>Uncontrolled arrhythmia</td>
<td>III-IV</td>
<td>Contraindication to travel</td>
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<tr>
<td>Controlled hypertension</td>
<td></td>
<td>Unrestricted travel</td>
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</tbody>
</table>

AST; altitude simulation test [2438m]. ¹British Thoracic Society (3), ²Aerospace Medical Association (1); ³American Thoracic Society (4), ⁴British Cardiac Society (65), ⁵Canadian Cardiac Society (58).
III-IV heart failure did not elicit angina, arrhythmia, or ischemia (2).

There are a number of potential interactions between cardiac and pulmonary disease that may contribute to exercise intolerance at altitude. Patients with cardiac failure and pulmonary hypertension typically have higher minute ventilation than healthy individuals at a given workload (6). Anemia, if present, has a significant effect because it reduces oxygen delivery for any given combination of lung function and cardiac output. Sarcopenia/cachexia is common in advanced heart and pulmonary disease (48). If present, the reduction in muscle bulk reduces maximal workload and decreases time to fatigue.

Generally it appears that travel to moderate altitude is safe in patients with stable cardiac disease who have good exercise tolerance at sea level. A broader question is whether the inevitable decline in exercise capacity at altitude will impair function in an individual to the extent that travel is not enjoyable. More data are needed to provide accurate advice for patients with severe cardiac disease of any form, and patients who are not stable should be cautioned not to travel to altitude.

**SUPPLEMENTAL OXYGEN**

On the basis of the physiology as reviewed in this article, guidelines have been established to assist physicians in determining who may be at risk from altitude exposure. These guidelines predominantly address the altitude that would be experienced during commercial aircraft travel (2,438 m, 8,000 ft). A summary of the current guidelines for patients with pulmonary and cardiac disease is presented in Table 3.

Supplemental oxygen is recommended for patients with pulmonary disease that may experience a PaO2 <50 mmHg in-flight (1, 3, 4) and in certain patients with moderate-severe cardiac disease (3, 58, 65) (Table 3). The advice is to maintain arterial oxygenation at altitude to the level at which the patient is clinically stable at sea level (4). It has been established that a flow rate of 2–3 l/min by nasal cannula at 2,438 m will clinically stabilize those who are not stable should be cautioned not to travel to altitude.

**SUMMARY**

When there is reduced reserve to adapt to hypoxic conditions at altitude, functional capacity is impaired by the failure to increase pulmonary gas transfer and/or cardiac output. This is commonly reflected in symptom-limited exercise impairment. Severe medical events appear to be infrequent; however, there is a paucity of epidemiological data addressing morbidity after travel to altitude and air travel in these patients. Unlike resting sea level arterial saturation, hypoxic altitude simulation testing predicts oxygenation at altitude. However, there is a clear need for further analysis of risk using additional physiological markers, both at rest and during mild exercise. Measures of pulmonary artery pressures, right heart function, and sympathetic activity may be more predictive of risk.

The three factors to consider when faced with questions regarding travel safety are the functional state at sea level, the altitude to be visited, and the anticipated additional workload from physical activity. Although the first two may be known, the third is unpredictable. Added to this is the fact that individual physiological responses to altitude vary. Presently it is difficult and impractical to assess these responses prior to travel.

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