Altitude-Related Hypoxia: Risk Assessment and Management for Passengers on Commerical Aircraft

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Mortazavi A, Eisenberg MJ, Langleben D, Ernst P, Schiff RL. ***Altitude-related hypoxia: risk assessment and management for passengers on commercial aircraft.*** **Aviat Space Environ Med 2003; 74: 922–7.**

Background: Individuals with pulmonary and cardiac disorders are particularly at risk of developing hypoxemia at altitude. Our objective is to describe the normal and maladaptive physiological responses to altitude-related hypoxia, to review existing methods and guidelines for preflight assessment of air travelers, and to provide recommendations for treatment of hypoxia at altitude. ***Data synthesis:*** Falling partial pressure of oxygen with altitude results in a number of physiologic adaptations including hyperventilation, pulmonary vasoconstriction, altered ventilation/perfusion matching, and increased sympathetic tone. According to three guideline statements, the arterial pressure of oxygen (P_{aO_2}) should be maintained above 50 to 55 mm Hg at all altitudes. General indicators such as oxygen saturation and sea level blood gases may be useful in predicting altitude hypoxia. More specialized techniques for estimation of altitude P_{aO_2}, such as regression equations, hypoxia challenge testing, and hypobaric chamber exposure have also been examined. A regression equation using sea level P_{aO_2} and spirometric parameters can be used to estimate P_{aO_2} at altitude. Hypoxia challenge testing, performed by exposing subjects to lower inspired F_{IO_2} at sea level may be more precise. Hypobaric chamber exposure, the gold standard, mimics lower barometric pressure, but is mainly used in research. ***Conclusion:*** Oxygen supplementation during air travel is needed for individuals with an estimated P_{aO_2} (8000 ft) below 50 mmHg. There are a number of guidelines for the pre-flight assessment of patients with pulmonary and/or cardiac diseases. However, these data are based on small studies in patients with a limited group of diseases.

Keywords: hypoxia, hypoxemia, altitude, air travel, COPD, oxygen, barometric pressure.

CLOSE TO TWO billion people travel in commercial airlines each year (33), including people with chronic cardiovascular and respiratory disease. In recent years, our knowledge of environmental conditions and mechanisms of physiological adaptation at high altitude has expanded. Hypoxia is one of the most important consequences of high altitude exposure. Most physicians do not use guidelines to assess their patients preflight (5). However, recognizing altitude-related hypoxia and oxygen requirements during air travel are of crucial importance in view of the frequent transportation of individuals with poor cardiopulmonary reserve. According to three guidelines statements, the P_{aO_2} at altitude should be maintained above 50–55 mm Hg at all times (25,26,36). This review will focus on the acute physiological responses to hypoxemia, the methods used in the preflight assesment of patients with cardiac and pulmonary disorders, and on current recommendations for assessment and treatment of hypoxia during air travel.

Environmental Conditions at High Altitude

Barometric pressure is defined as the pressure on an object from the atmospheric layers above. This pressure decreases exponentially with increased distance above the earth's surface. According to Dalton's law, the barometric pressure exerted by a mixture of nonreacting gases, such as atmosphere, is equal to the sum of the partial pressures of the separate components. The proportion of atmospheric oxygen remains constant at 21% at altitudes below 100,000 m. Therefore, the partial pressure of oxygen (P_{O_2} = barometric pressure $\times$ 0.21) falls substantially with lower barometric pressure at higher altitude. P_{O_2} at sea level is 159 and decreases by 50% at 5496 m. For each additional 300 m, P_{O_2} decreases a further 4–5 mm Hg (13).

A decrease in barometric pressure also leads to expansion of gases in accordance with Boyle's law. At 5486 m (0.5 atm), the volume of an enclosed gas will be twice as large as if it were exposed to sea level (1 atm). Clinically, this can have implications with gas trapped in body cavities including sinuses, middle ear, gastointestinal tract, pleural cavity, and eye.

Aircrafts usually cruise between 6500 and 13,500 m above sea level (22,000 to 44,000 ft). Hypoxic and hypobaric conditions would be lethal at these altitudes without pressurization of the aircraft cabin. For pressurization, air is compressed in the aircraft to obtain a cabin pressure equivalent to that found at 1500 to

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This manuscript was received for review in May 2002. It was revised in January and March 2003. It was accepted for publication in April 2003.

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Dr. Eisenberg is a Physician-Scientist at the Quebec Foundation for Health Research supported in part by the Bank of Montreal.

2500 m of altitude (5000 to 8000 ft). This is called a "cabin altitude" of 1500 to 2500 m. If necessary, cabin pressure can be reduced to that of sea level by flying below 7000 m (23,000 ft). Newer aircraft may fly at higher altitudes exposing passengers to a more hypoxic environment (6).

Commercial air carriers generally maintain a cabin altitude below 2500 m (8000 ft). The Federal Aviation Administration (FAA) requires supplemental oxygen to be available for passengers if operating at flight altitudes >3000 m (10,000 ft) (15–18). Importantly, cabin environment has very low humidity (usually <25%) and if supplied for long periods, oxygen should always be humidified.

Acute Responses to Altitude Hypoxia

The steps required for oxygen transportation from ambient air to peripheral tissues include alveolar ventilation, matching of pulmonary ventilation with blood perfusion, diffusion of oxygen through the alveolar-capillary membrane, oxygen binding to hemoglobin, blood circulation, and diffusion into peripheral tissues. Compensatory mechanisms to acute altitude hypoxia occur for each step in the process of oxygen delivery to tissues. Most knowledge of high altitude physiology has been acquired through studies of mountain climbers.

Hyperventilation is the first compensatory mechanism to altitude hypoxia. As discussed previously, the alveolar oxygen pressure (P_{AO_2}) is a direct reflection of barometric pressure, while the alveolar carbon dioxide pressure (P_{ACO_2}) inversely reflects alveolar ventilation. When barometric pressure decreases, ventilation increases to compensate for the drop in alveolar oxygen pressure. As a consequence, alveolar carbon dioxide decreases as well (38). The reduction of arterial carbon dioxide pressure (P_{aCO_2}) inhibits the ventilatory drive and is one of the factors which limits the hypoxic ventilatory response. Hyperventilation also results from hypoxic stimulation of chemoreceptors of the carotid arteries and aorta (which can also be stimulated by an increase in P_{aCO_2} and a decrease in arterial pH). These chemoreceptors activate the respiratory centers in the midbrain responsible for increased ventilation (8,27,38). The increased minute ventilation results primarily from an increase in tidal volume rather than from an increased respiratory rate (38). Ventilation increases abruptly during the first minutes to hours following the ascent in altitude and then continues to rise gradually over days. One hypothesis for this response is that the initial respiratory alkalosis limits the extent of hyperventilation. Once renal compensation with bicarbonate loss occurs over several days, ventilation is able to increase gradually.

Ventilation-perfusion relationships are also affected by ascent to high altitudes. The initial hyperventilation is matched to increased cardiac output and pulmonary perfusion (27). As well, hypoxia and secondary pulmonary vasoconstriction redistribute the blood flow to lung regions poorly perfused at sea level, which improves the ventilation-perfusion matching.

Diffusion of oxygen through the alveolar-capillary membrane worsens at high altitudes. Oxygen flux is dependent on the pressure gradient between alveolus and capillary, among other factors. This equilibrium is time dependent; therefore, as P_{AO_2} decreases with altitude, pulmonary transit time may not be adequate for equilibrium of oxygen to occur, a phenomenon called diffusion-limitation of oxygen transfer at high altitude. Diffusion limitation is exacerbated by exercise, when pulmonary capillary transit time is shortened and mixed venous P_{O_2} falls further. Studies of climbers on Mount Everest confirmed that hypoxemia at high altitude is mainly due to diffusion-limitation rather than ventilation-perfusion mismatching (39).

Cardiac output increases initially in a linear manner with hypoxemia to help sustain oxygen delivery in spite of a decrease in arterial oxygen content. The increase in cardiac output is mainly secondary to increased heart rate (adrenergic response), with minimal changes in stroke volume (1). Within minutes to hours of acute hypoxemia, the cardiac output decreases gradually toward baseline (29), and in a few days to weeks at high altitude, the cardiac output reaches the baseline level (38). Systemic vascular resistance increases leading to a small rise in BP. Pulmonary vascular resistance increases at high altitude as a result of pulmonary vasoconstriction secondary to hypoxia (38).

Maladaptation in Individuals at Risk

Medical emergencies during air travel are very uncommon, occurring in 1 per 14,000 to 40,000 passengers (9,33,35). Cardiac, respiratory, and neurologic problems make up the most serious events and account for the majority of instances requiring an unscheduled landing (20). The incidence of death among air travelers is extremely low at approximately 0.3–1 per 3,000,000 travel episodes (9,20,34,35). Cardiac etiology is the most frequent cause of in-flight deaths (23).

As mentioned earlier, lower P_{O_2} due to the lower barometric pressure leads to relative hypoxia in all people who travel by air. For most people, this reduction in arterial oxygen pressure (P_{aO_2}) only represents a small reduction in oxygen carrying capacity in blood as the P_{aO_2} lies on the flat part of the oxyhemoglobin dissociation curve. However, in patients with cardiopulmonary disease with a lower baseline P_{aO_2}, the drop in P_{O_2} at 2500 m can cause a dramatic fall in oxygen saturation as the P_{aO_2} is on the steep part of the curve. Therefore, patients with pulmonary disease (decreased capacity of oxygen uptake), cardiovascular disease, or anemia (decreased oxygen transportation capacity) may develop disorders related to decreased oxygen supply to peripheral tissues (**Fig. 1**). Hypoxemia may manifest with altered mental status, dizziness, blurred vision, personality changes, and coma.

In addition to the danger of hypoxia in COPD, patients with bullous disease are theoretically at increased risk of pneumothorax due to gas expansion at lower barometric pressure. The volume of gas in a non-communicating bulla will increase by 30% on ascent from sea level to 8000 ft.

The sympathetic response to hypoxia compounded with lower arterial oxygen can have significant impli-

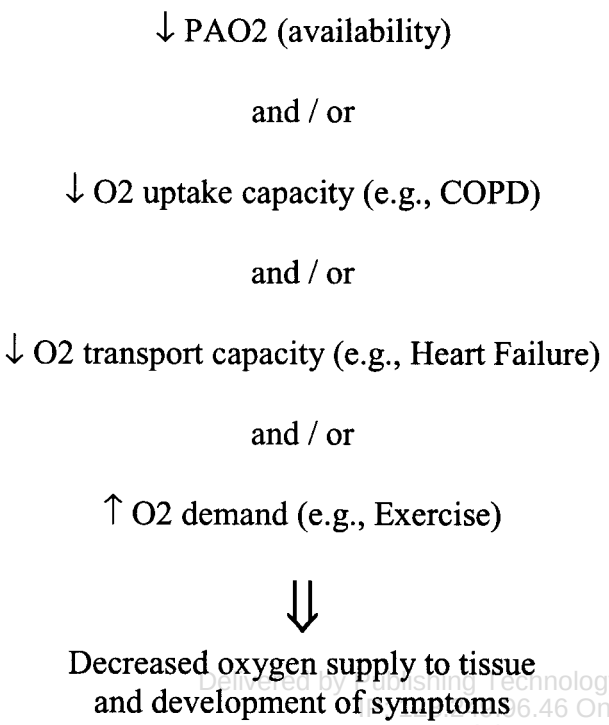

Fig. 1. Exposure to altitude and pathophysiologic responses in patients with cardiopulmonary disorders. Adapted from: Gong H. Air travel and oxygen therapy in cardiopulmonary patients. Chest 1992; 101: 1104–13.

cations for cardiac patients. Increased myocardial oxygen demand and/or decreased oxygen supply can aggravate unstable angina. The sympathetic output can also increase venticular ectopy. However, to our knowledge, there has been no study which has demonstated an increase in significant ventricular arrythmias.

High-altitude syncope is a well documented phenomenon. Although the mechanisms involved in hypoxia-related syncope are not fully identified, the sudden episodes of bradycardia with hypotension are best explained by activation of the Bezold-Jarisch reflex and increased vasodilator response to epinephrine via β adrenoreceptors (19,24,40). The Bezold-Jarisch reflex is an inhibitory reflex originating from mechanoreceptors located in the heart which leads to suppression of sympathetic activity and relative augmentation of parasympathetic activity.

Recommendations for Patient Assessment

According to the British Thoracic Society, the following patients should have pre-flight assessments (25):

- Severe COPD or asthma
- Severe restrictive disease (including chest wall and respiratory muscle disease), especially with hypoxemia and/or hypercapnia
- Cystic fibrosis
- History of air travel intolerance with respiratory symptoms (dyspnea, chest pain, confusion, or syncope)
- Co-morbidity with other conditions worsened by hypoxemia (cerebrovascular disease, coronary artery disease, heart failure)
- Pulmonary tuberculosis
- Within 6 wk of hospital dischrage for acute respiratory disease
- Recent pneumothorax
- Risk of/or previous venous thromboembolism
- Pre-existing requirement for oxygen or ventilator support

We believe the following patients should also have preflight assessments:

- Patients with poorly controlled hypertension
- Patients with ventricular ectopy/arrythmias

More specific recommendations for cardiac patients have been proposed regarding cardiac contraindications to travel and recommendations for air travel following myocardial infarction. Strong contraindications to air travel by coronary patients include (1):

- New onset angina
- Unstable angina, particularly angina at rest
- Poorly controlled congestive heart failure
- Frequent/high grade ventricular ectopy
- Severe/poorly controlled hypertension

Travel following uncomplicated myocardial infarction (MI) has been the subject of a few small studies which concluded that the risk of adverse events is small by 2–3 wk post-infarction, provided that the patient is stable, without persistent angina, arrhythmia, or congestive heart failure (7,14,31,41). The American College of Cardiology and American Heart Association recommend that following uncomplicated MI, air travel should be undertaken only by stable patients (without a fear of flying) within the first 2 wk, and then only as long as they travel with companions, carry sublingual nitroglycerin, and request airport transportation to avoid rushing (32). Unstable, symptomatic, or patients who experience a complicated MI (requiring CPR, experiencing hypotension, serious arrhythmias, high-degree block, or congestive heart failure) should be stabilized for at least 2 wk before commercial air travel (32).

Methods of Patient Assessment

Preflight assessment for altitude-related hypoxia consists of initial screening procedures, followed by more specific testing as required. These may include using regression equations to predict altitude P_{aO_2}, hypoxia challenge testing, or hypobaric chamber exposure in experimental settings.

Initial screening of all patients should consist of a history (including previous flying experience), physical examination, spirometry, and measurement of oxygen saturation by pulse oximetry. Measuring ground level arterial blood gases is indicated with known or suspected hypercapnia.

Sea level oxygenation, based on either pulse oximetry or arterial blood gases, have been used to guide the need for further investigation of altitude-related hypoxia. The British Thoracic Society (BTS) recommends pulse oximetry in its evaluation. According to the BTS, if oxygen saturation is <92% at ground level, oxygen is required at altitude. If oxygen saturation is above 92%

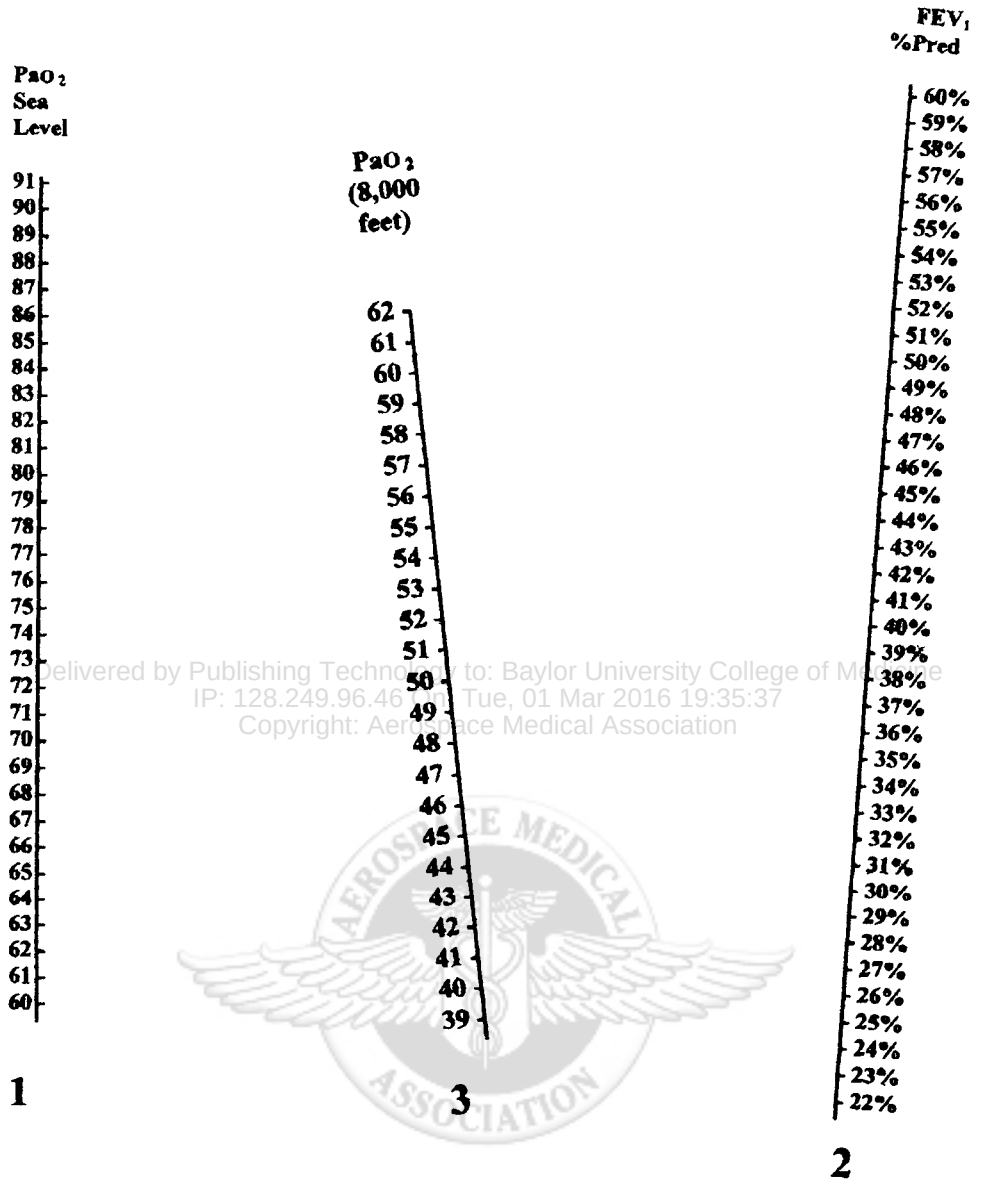

Fig. 2. Chart for estimation of P_{aO_2} at 8000 ft. Nomogram for estimating P_{aO_2} during air travel based on P_{aO_2} at sea level is used by placing a ruler on P_{aO_2} at sea level (column1) and aligning with FEV_1 percent predicted (column 2), then reading P_{aO_2} during air travel (column 3). From Dillard TA, Ewald F. The use of pulmonary function testing in piloting, air travel, mountain climbing, and diving. Clin Chest Med 2001; 22:803.

without associated risk factors, no oxygen is required and the patient can fly safely without additional tests. These risk factors include $FEV_1 < 50\%$ predicted, lung cancer, restrictive disease (including chest wall, parenchymal, and respiratory muscle disease), cerebrovascular or cardiac disease, or within 6 wk of a COPD exacerbation. If oxygen saturation is 92–95% with any of the above risk factors, further testing is required.

Alternatively, measurement of arterial blood gases alone may be useful since ground-level P_{aO_2} is thought to be the best predictor of P_{aO_2} at high altitude by some authors (26). According to these authors a ground-level P_{aO_2} above 70 mm Hg is considered sufficiently high to preclude hypoxemia (P_{aO_2} less than 50 mm Hg) at cabin altitude (26). However, the accuracy of such a prediction has been questioned in a recent study (4). In their study, Christensen et al., exposed 15 COPD patients with $FEV_1 < 50\%$ predicted and sea level P_{aO_2} above 70 mm Hg to an altitude pressure of 2438 m (8000 ft) in a hypobaric chamber. They found that a significant number of these subjects developed hypoxemia (P_{aO_2} less than 50 mm Hg). The hypoxemia was aggravated with light exercise equivalent to walking in the aircraft. Importantly, the hypoxic patients were asymptomatic (3,4).

Once a patient at risk for significant altitude-related hypoxia is identified, the two approaches used to assess the extent of hypoxia are predictive equations and hypoxia challenge testing. Dillard et al. (11) conducted a meta-analysis of five small studies predicting the severity of hypoxia during air travel in COPD patients. They found that both baseline P_{aO_2} and FEV_1 are good indicators of high altitude P_{aO_2}. They then developed a chart which predicts P_{aO_2} at 8000 ft (2438 m), based on sea level P_{aO_2} and FEV_1 (10) (**Fig. 2**). Dillard et al. (12) also developed a regression equation to predict P_{aO_2} at

8000 ft, which provides comparable prediction of P_aO_2 as measured by the hypoxia challenge test in normal subjects and in those with chronic obstructive pulmonary disease (12):

P_aO_2 (8000 ft) = 0.238 (P_aO_2-Sea Level) + 20.098 (FEV_1/FVC) + 22.258

where FEV_1 is the forced expiratory volume in first second; and FVC is the forced vital capacity.

If estimates of P_aO_2 are close to 50 (±3) mm Hg, a hypoxia challenge test should be considered for further evaluation. The altitude of 8000 ft was chosen as it is the highest cabin altitude generally flown by commercial airlines. One of the limitations of these predictive equations is that they are based on a small set of selected patients (in this case the majority were men with COPD), and may not correlate with different subsets of patients with respiratory disease. Indeed, a small study of 28 patients found that hypoxia as demonstrated by the hypoxia challenge test was not predicted by FEV_1 or pretest oxygen saturation (30).

The hypoxia challenge test, originally described by Gong et al., consists of breathing a hypoxic gas mixture at sea level to simulate barometric hypoxia at altitude (21). Simultaneous EKG tracing is used to document ventricular ectopy or arrhythmias. As well, patients are evaluated for symptoms such as dyspnea and chest pain, though it is rare for patients to develop symptoms during testing. A cabin altitude of 8000 ft is simulated by breathing 15% inspired oxygen at sea level. The gas mixture can be delivered with a non-rebreathing valve with a mouthpiece or tight fitting mask, a 35% Venturi mask, or by filling a body box. Although 10 min is sufficient for inspired gas to reach mass equilibrium, it may be too brief to assess the full physiologic effect of hypoxia; therefore, a 20 min exposure is favored (13). Arterial blood gases record the P_aO_2 after 20 min. Guidelines recommend in flight oxygen for $P_aO_2 < 50$ (25,36) or oxygen saturation < 85% (25). These figures, however, are arbitrary with little supporting evidence. One limitation of hypoxia challenge testing is that the lower F_IO_2 is administered at sea level and the absence of hypobaric conditions may alter the symptoms which would occur at altitude.

The ideal method of predicting P_aO_2 at high altitude is hypobaric chamber exposure. This method consists of exposing subjects to a depressurized environment similar to that found at altitude. However, this method is not widely available, is an impractical method for preflight assessment, and provides results comparable to hypoxia challenge testing according to some data (12).

One must be aware that most studies of hypoxia in air travel and preflight assessment have been performed on patients with COPD. These results and recommendations, however, are being generalized to a wide group of patients including those with bronchiectasis, cystic fibrosis, interstitial lung disease, pleural effusion, pulmonary vascular disease, neuromuscular disease, hypoventilation syndromes, kyphoscoliosis, and cardiac patients (26,28). Further studies must be conducted on these subsets of patients as their requirements may be different.

Treatment

Treatment of altitude-related hypoxia includes supplemental oxygen, as well as preventive measures such as continuation of usual medications, adequate hydration, avoidance of respiratory depressants, and ambulation.

Supplemental oxygen is the most effective treatment of high altitude hypoxia and is available in commercial aircrafts (37). The lack of regulations explains why there is a great variation in availability, cost, and ease of implementation of in-flight oxygen among commercial airlines (37). The FAA requires a physician's statement of oxygen need and dosage in order for a patient to receive continuous oxygen during flight. Generally 2 $L \cdot min^{-1}$ of oxygen by nasal cannula is an adequate supply for patients with reversible ventilation-perfusion mismatch who do not require oxygen at ground level, when flying at a cabin altitude of 8000 ft or less (2). Supplemental oxygen should be humidified and administered once at cruising altitude. It should be used both at rest and during ambulation of subjects on board as the risk of blood oxygen desaturation is greater with exercise (2,4). In all cases of refractory hypoxemia in air, sea level cabin pressure can be obtained by flying the aircraft below 7000 m (≈ 23,000 ft).

In addition, the following prophylactic measures should be implemented. Patients with cardiopulmonary disease should take all their usual medications during air travel, and should have a supply of all medications with them including preventive and relieving inhalers. Those with abundant respiratory secretions must continue oral hydration. Treatment with almitrine biomesylate which increases the P_aO_2 of COPD patients at ground level is controversial (22). Almitrine stimulates the chemoreceptors in the carotid and aortic bodies, thereby increasing respiration. Sedatives and excess alcohol should be avoided as they may blunt the hyperventilatory response to hypoxia. Frequent ambulation should be considered in subjects with prolonged immobilization in the aircraft to minimize the risk of deep venous thrombosis.

CONCLUSIONS

Altitude related hypoxia can have significant implications in patients with cardiorespiratory diseases. Guideline statements from the American Thoracic Society, the British Thoracic Society, and the Aerospace Medical Association recommend maintaining the in-flight P_aO_2 above 50–55 mm Hg at all times (25,26,36). If a drop of P_aO_2 below these levels is anticipated, in-flight oxygen should be supplemented (2,26). Sea level oxygen saturation is a good initial screening test. In cases of oxygen saturation between 92–95% at sea level with risk factors, additional investigations with predictive equations and/or hypoxia challenge testing can help decide on the need for in flight oxygen (25). However, these tests may be imperfect, especially for patients with respiratory disease aside from COPD. Cardiac patients are also at risk of ischemia and arrhythmia due to hypoxia itself and its resultant activation of the sympathetic system. New onset or unstable angina, poorly

controlled congestive heart failure, and high grade ventricular ectopy are contraindications for air travel as they increase the risk of adverse events at altitude. Stable patients following uncomplicated myocardial infarction can safely travel within 2 wk of the event. Further studies, including those done with patients with diverse cardiorespiratory diseases as well as studies done at altitude, would help validate current recommendations.

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