To Fly Or Not To Fly? Aviation and Respiratory Diseases

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ABSTRACT For most passengers, even those with respiratory disease, air travel is safe and comfortable. Some travelers may experience hypoxia at sea level but may not need supplemental oxygen during air travel in a hypobaric hypoxic environment. For some individuals compensatory pulmonary mechanisms may be inadequate, causing profound hypoxia. In addition, venous thromboembolism/pulmonary emboli may occur, especially during long haul flights. With adequate screening, patients at risk can be identified, therapeutic solutions can be proposed for the flight, and most can travel safely with supplemental oxygen and/or other preventive measures.

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Air travel is often the first choice of travel. It is fast and practical and is becoming less expensive. Commercial air travel is very popular in Israel with more than 24.8 million passengers and nearly 168,000 flights passing through Ben Gurion Airport in 2019 [1].

It is estimated that over one billion passengers travel by air worldwide each year, and for the majority this is without risk. With the emergency of coronavirus disease-2019 (COVID-19) pandemic air travel was shut down worldwide for many weeks and started again in summer of 2020. Over 30 years ago it was already estimated that 5% of commercial airline passengers were ambulatory patients with some illness including chronic obstructive pulmonary disease (COPD). With new ultra-long haul flights, passengers are exposed to cabin altitudes of up to 2450 meters for sometimes longer than 20 hours [2]. Longer journeys increase the odds of in-flight medical incidents and physiological disturbances associated with moderate but prolonged hypoxia, prolonged immobility, and protracted exposure to reduced barometric pressure [3].

Most of the patients with chronic lung disease tolerate long-distance air travel, which is generally safe

Due to the ageing population, the number of passengers with pre-existing medical conditions is expected to increase. Since air travel resumed in most countries, it has become mandatory for all the passengers to travel with a mask covering the mouth and the nose. Before the COVID-19 pandemic, in-flight medical events (IFMEs) were found to occur at a rate of approximately 15 to 100 per million passengers, with a death rate of 0.1 to 1 per million [4]. The most common problems were syncope or presyncope (37.4% of cases), respiratory symptoms (12.1%), and nausea or vomiting (9.5%). Most of those in-flight emergencies, approximately 65%, are due to a pre-existing medical condition [5]. Commercial aircraft fly at 11500 meters, but are pressurized to a cabin altitude of 2450 meters. Variations in cabin altitude, up to 2717 meters, have been reported [6]. The reduced alveolar oxygen partial pressure (PaO2) at this altitude equates to breathing 15% oxygen at sea level and thus lowers the PaO2 of a healthy passenger depending on age and minute ventilation between 8 and 10 KPa (60–75 mmHg). Oxygen saturation measured by pulse oximetry (SpO2 89–94%) when exercising or sleeping may even be lower. Altitude may worsen hypoxemia in pulmonary disease. The physiological compensation for acute hypoxemia is mild to moderate hyperventilation, in addition to a fall in arterial carbon dioxide tension (PaCO2) and a moderate tachycardia.

This physiological compensation, limited by the shape of the hemoglobin dissociation curve, usually goes unnoticed [Figure 1]. However, this exposure may have a profound effect on those with lung disease, especially if they are hypoxemic at sea level, because the steeper part of the dissociation curve is involved [Figure 2].

Other consequences of air travel include immobility, predisposing to venous thrombosis, increased gas volumes, lowered humidity, and potential for transmission of infection.

Efforts should be made to locate patients who may need supplemental oxygen and or continuous positive airway pressure and those who may need anticoagulant prophylaxis

The other main effect of altitude is Boyle's law, which states that the volume of gas varies inversely with the surrounding pressure at constant temperature. One liter of gas at sea level will expand to approximately 1.4 liters at an altitude of 2450 meters [7]. This is clearly only of medical relevance if gas is trapped in a confined space such as the pleural cavity, the middle ear, or in a body cavity after surgery.

Table 1. Disease specific recommendations

Disease	Consideration	Recommendation
Asthma and COPD	Acute exacerbation during flight Severe asthma or COPD (FEV1 < 30%)	Give patient's own bronchodilator Consult Specialist beforehand Bring supply of prednisone
Bronchiectasis	General	Nebulized antibiotics and bronchodilators are not required
Interstitial lung disease	General	Careful assessment of patients Consider oxygen supplementation Supply of antibiotic and prednisone
Pulmonary hypertension	General	NYHA class III-IV should receive in flight oxygen NYHA class IV with severe pulmonary hypertension should avoid flying
Obstructive sleep apnea	General CPAP device	Avoid alcohol and sedatives Dry cell batteries, operable device at all altitude

Adopted from the summery of British Thoracic Society 2011 guidelines
COPD = chronic obstructive pulmonary disease, CPAP = continuous positive airway pressure, NYHA = New York Heart Association

Neither resting sea level oxygen saturation nor forced expiratory volume in 1 second (FEV1) reliably predicts hypoxemia or complications of air travel in passengers with respiratory disease. There is no reliable threshold in these variables to determine accurately the safety of air travel or need for in-flight oxygen in an individual patient [8-11].

Patients with chronic lung disease may have mild hypoxemia at sea level that may go unrecognized. Even among hypoxemic patients, some do not need supplemental oxygen. During air travel in a hypobaric hypoxic environment, the compensatory pulmonary mechanisms may be inadequate in patients with lung disease despite normal sea-level oxygen requirements. In addition, compensatory cardiovascular mechanisms may be less effective in some patients who are unable to increase cardiac output [12].

Patients with cystic lung disease may also be at increased risk of pneumothorax. Reported incidence of spontaneous pneumothorax not associated with air travel in the general population ranges from 7 to 18/100,000 per year for males and 1 to 6/100,000 per year for females. The exact incidence of pneumothorax during commercial air travel is unknown due to non-standardized reporting requirements for in-flight medical emergencies, difficulty in making an in-flight diagnosis, and possible delay in symptoms. However, in-flight pneumothorax must be rare, because it is not mentioned in most reports addressing in-flight emergencies [13].

Should pneumothorax occur, it could present a significant challenge to the patient, particularly if hypoxemia is already present. As such, a thorough evaluation should be conducted on patients with chronic lung disease and cardiac disease who are planning air travel. The duration of the planned flight, the anticipated levels of activity, co-morbid illnesses, and the presence of risk factors for venous thromboembolism are important considerations. Hypobaric hypoxic challenge testing reproduces an environment most similar to that encountered during actual air travel; however, it is not widely available. Assessment for hypoxia is otherwise best performed using a normobaric hypoxic challenge test. Patients who require supplemental oxygen need to contact the airline and request this accommodation before the flight. They should also be advised on arranging portable oxygen concentrators before air travel, and a discussion of the potential risks of travel should take place.

In the COVID-19 era, keeping social distance and wearing face masks (N95 are preferable) is important

PATIENTS FOR WHOM AIR TRAVEL IS CONTRAINDICATED

Certain patients with pulmonary disease should be instructed not to fly, including patients presenting with active infectious diseases (e.g., tuberculosis [14], documented COVID-19 infection [15]) or those for whom air travel would pose a risk to themselves: hemoptysis, unresolved pneumothorax with persistent air leak [16], and a sea-level supplemental oxygen requirement in excess of 4 L/minute.

Other non-respiratory contraindications for air travel include severe sinusitis, large obstructing polyps, recent nasal or facial surgery, and severe recurrent epistaxis [2].

RECOMMENDATIONS FOR INTERNATIONAL TRAFFIC RELATED TO COVID-19

Many countries have halted some or all international travel since the onset of the COVID-19 pandemic but now have plans to re-open travel, WHO recommends that priority should be given to essential travel for emergencies, humanitarian actions (including emergency medical flights and medical evacuation), travel of essential personal and repatriation, and cargo transport for essential medical, food, and energy supplies [Table 1] [17]. In general, evidence has shown that restricting the movement of people and goods during public health emergencies is ineffective in most situations and may divert resources from other interventions. Travel bans to affected areas or denial of entry to passengers coming from affected areas are usually not effective in preventing the importation of cases but

Figure 1. Relationship between cabin altitude and calculated alveolar oxygen tension (PaO2) in a person with normal PaO2 at sea level, an individual at risk with decreased PaO2 that is within normal limits, and an individual with a PaO2 at sea level that would be associated with significant hypoxemia. Also indicated are altitude thresholds whereby pilots, air crew, and healthy passengers are required to use supplemental oxygen as per U.S. Federal Aviation Administration regulations

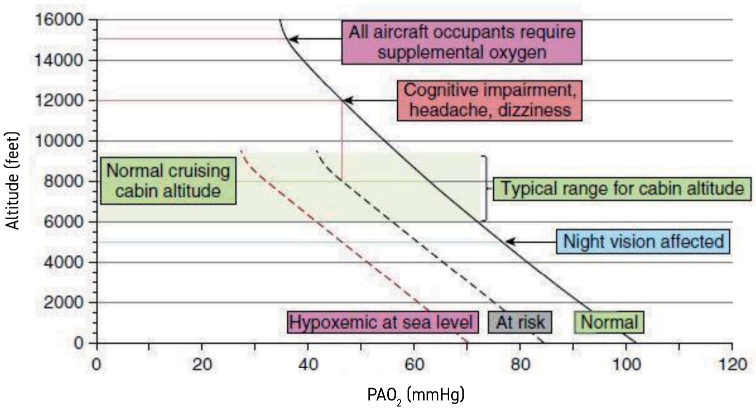
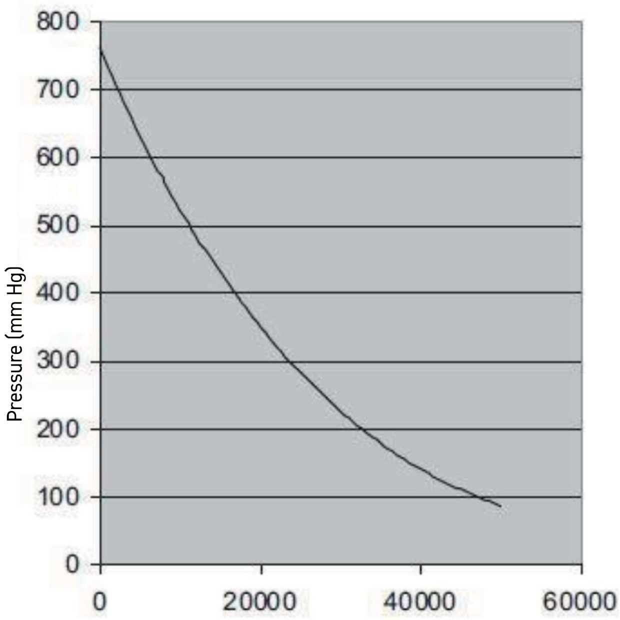


Figure 2. Relationship between atmospheric pressure (mmHg) and altitude (feet)



may have a significant economic and social impact.

Travelers who are sick should delay or avoid travel to affected areas, in particular elderly travelers and people with chronic diseases or underlying health conditions. General recommendations for personal hygiene, cough etiquette, and social distancing of at least one meter between people showing symptoms remain particularly important for all travelers.

Travelers returning from affected areas should self-monitor for symptoms for 14 days and follow national protocols of receiving countries. Some countries may require returning travelers to enter quarantine. If symptoms occur, such as fever, or cough or difficulty breathing, travelers are advised to contact local health care providers, preferably by telephone, and inform them of their symptoms and their travel history [14] [Appendix 1]. To date, there are few publications of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) transmission during flights.

The U.S. Department of Health and Human Services air medical evacuation teams repatriated more than 2000 individuals who were either exposed to or had confirmed/suspected COVID-19 on 39 flights without any crew getting infected. This result was attributed to face masks being worn by everyone (including N95 masks for known positives), safe work practices, and high-grade personal protection equipment for the crew. There are significant associations between the use of face masks (especially N95 masks rather than disposable surgical masks), eye protection with a face shield, and physical distancing of more than 1 meter and reductions in SARS-CoV-2 transmission [18].

Patients with suspected COVID-19 can infect others at any time, including during transfer and transport. As COVID-19 is a new infectious disease, lapses in infection prevention and control can easily happen at vulnerable moments such as during transfer. Clear delineation of roles and responsibilities as well as minimum standards should be maintained.

The current COVID-19 pandemic highlights the challenges air ambulance services are facing when transporting highly infectious patients for several hours in enclosed spaces. There are different methods used by several organizations in Europe in transporting these patients. Possible benefits of the use of small patient isolation units allow changing the means of transport without contaminating the surroundings and while still allowing access to the patient [19].

AIRWAY DISEASE: ASTHMA, COPD, BRONCHIECTASIS

Data on patients with COPD are limited. Compared to healthy individuals, passengers with moderate to severe COPD have a higher risk of experiencing significant hypoxemia during air travel. In addition, they are at risk of developing high levels of carboxyhemoglobin resulting from smoking and may experience expansion of non-functioning emphysematous bullae and abdominal gases, which could further compromise lung function. Those patients with large bullae are theoretically at increased risk of pneumothorax as a result of volume expansion at reduced cabin pressures. The volume of gas in a non-communicating bulla will increase by 30% on ascent from sea level to 2438 meters [17].

Progressive hypoxia induces mild hyperventilation results in small but significant reductions in PaCO2 [20]. Hypoxemia-induced hyperventilation, in turn, may result in hyperinflation and, therefore, increased intrinsic positive end-expiratory pressure, which is mainly responsible for respiratory muscle fatigue in severe COPD especially during long-haul flights. With optimized care, patients can fly with only minimal additional risk. Clinical and functional evaluation for fitness to fly and possible risk factors for in-flight hypoxemia should be assessed in all COPD patients before flying.

In one study [18] COPD patients were assessed by a respiratory function test before the flight. Pulse oximetry, cabin pressure, and dyspnea were recorded in flight. Post-flight hypoxia inhalation test (HIT) and 6-minute walk tests were performed. All passengers flew without the use of oxygen and no adverse events were recorded in-flight (mean cabin altitude 2165 meters, altitude range 1892 to 2365 meters). Air travel caused significant desaturation (mean preflight oxygen saturation 95 ± 1%, mean in-flight oxygen saturation 86 ± 4%), which was exacerbated by activity (nadir pulse oximetric saturation [SpO2] 78 ± 6%). The HIT caused mean desaturation that was comparable to that of air travel (84 ± 4%). The mean in-flight partial pressure of inspired oxygen (PIO2) was higher than the HIT PIO2 (113 ± 3 mmHg vs. 107 ± 1 mm Hg, respectively; $P < 0.001$). The HIT SpO2 showed the strongest correlation with in-flight SpO2, so it seems reasonable to conclude that many patients tolerate significant hypoxemia without any symptoms or an adverse event.

Proactive strategies to identify patients at risk and implementing preventive measures for adverse events in high-risk patients should be encouraged to achieve better disease management [19].

ASTHMA

The commercial flight environment does not usually pose problems for those with asthma. The main risk is of bronchospasm induced by bronchial mucosal water loss resulting from low cabin humidity. Hypobaric hypoxia should not present a significant risk, and reduced cabin ambient pressure should not affect patients with no co-morbidity.

There are no data available to predict when it is safe to fly after an acute asthma attack. It would be prudent for any passenger with well-controlled asthma to take their regular preventer and reliever medicines on board [20].

BRONCHIECTASIS

Nebulized antibiotics or nebulized bronchodilators should not be required.

PULMONARY ARTERY HYPERTENSION

Pulmonary artery pressure increases due to hypoxic vasoconstriction during air travel, even in healthy individuals without any pre-existing cardiopulmonary disease [21]. Increase in pulmonary artery pressure is more pronounced in COPD patients with pre-existing pulmonary hypertension and in patients with known pulmonary artery hypertension (PAH). This condition might lead to an increase in right ventricle after load and eventually right ventricular dysfunction with increased myocardial oxygen demand and hemodynamic compromise.

Hypoxemia is common among people with PAH traveling by air, occurring in 1/4 people studied. Hypoxemia is associated with lower cabin pressures, ambulation during flight, and longer flight duration. Patients with PAH who travel on flights of longer duration or who have a history of oxygen use, including nocturnal use only, should be evaluated for supplemental in-flight oxygen [22].

PNEUMOTHORAX

Patients with a closed pneumothorax should not travel on commercial flights. Patients who had a pneumothorax must undergo a chest X-ray to confirm resolution before flight. Many physicians suggest waiting an additional 7 days before embarking upon flight. In the case of a traumatic pneumothorax, the delay after full radiographic resolution should ideally be 2 weeks.

A definitive surgical intervention undertaken via thoracotomy is likely to be entirely successful and patients should be allowed to fly once they have recovered from surgery. A similar intervention undertaken by video assisted thoracoscopic surgery is also expected to have a high success rate, but is not definitive. These patients should be aware of a slight risk of recurrence. Patients having other forms of pleurodesis and those not undergoing pleurodesis after a pneumothorax are unlikely to have further episodes precipitated by flight, but spontaneous recurrence could have important consequences in the absence of prompt medical care. The risk of recurrence is higher in those with coexisting lung disease and does not fall significantly for at least 1 year. Those not undergoing definitive surgery may therefore consider alternative forms of transport [16].

The incidence of pneumothorax in patients with lymphangioleiomyomatosis is about 1000 times higher than in the general female population and therefore, any unusual clinical symptoms such as chest pain or breathlessness should preclude air travel until fully evaluated. Chemical or surgical pleurodesis partly reduces the risk of PT recurrence in LAM [23].

INTERSTITIAL LUNG DISEASE

Data remains limited on interstitial lung disease (IDL). ILD patients will experience desaturation and tachypnea while staying at high altitude destinations and are more likely to require emergency medical care after air travel. In those patients, neither FEV1 nor resting SpO2 predict desaturation at high altitudes [24].

OBSTRUCTIVE SLEEP APNEA AND OBESITY

Little is known about obstructive sleep apnea (OSA) and air travel. Patients are advised to avoid alcohol before and during flight because of the adverse effects of alcohol on sleep and OSA. Sleeping medications and sedatives should also be avoided. Flights may be scheduled overnight. Evidence suggests that withdrawing continuous positive airway pressure (CPAP) for just 1 day may cause sleepiness. Patients after trans-meridian flights may also suffer from jetlag. It is advisable for patients to use CPAP while sleeping in-flight (having notified the airline in advance) [24,25].

The association of Obesity and OSAS is well-known. Obesity may cause dyspnea, chronic hypoventilation (obesity hypoventilation syndrome), and complicate COPD (overlap syndrome). It is also a risk factor for VTE. There is little data on the effects of air travel in obese passengers [26].

PULMONARY EMBOLISM

Air travel is considered a risk factor for pulmonary embolism and has been termed "economy-class syndrome" [27,28]. Immobility, aggravated by the limited space in economy class, is assumed to be responsible for this risk.

The incidence of pulmonary embolism is much higher among passengers traveling more than 5000 km (1.5 cases per million, as compared with 0.01 case per million among those traveling less than 5000 km). The incidence of pulmonary embolism was 4.8 cases per million for those traveling more than 10,000 km [29].

Passengers with minor signs, such as mild-to-moderate chest pain, fever, or calf pain, may leave the airport without medical consultation and thus without a diagnosis. Several reports have suggested that pulmonary embolism may develop in passengers up to several weeks after air travel [30]. The percentage of cardiac arrests that occur in flight or immediately after landing that might be attributable to pulmonary embolism is unknown [31,32]. Physicians should make decisions on an individual case-by-case basis as the evidence for any particular recommendation is limited and firm guidelines cannot be formulated.

AIRBORNE INFECTIONS

Pre-flight assessment is advised for those with acute infection. Patients with infectious tuberculosis or active COVID-19 infection, or individuals who require quarantine due to close contact with a COVID-19 patient, must not travel by public air transportation. The World Health Organization (WHO) guidelines state that physicians should inform all infectious and potentially infectious tuberculosis patients that they must not travel by air on any commercial flight of any duration until they are sputum smear-negative on at least two occasions. However, patients in whom drug-resistant tuberculosis is not suspected and who have completed 2 weeks of effective antituberculous treatment are generally considered non-infectious. Patients with multi-drug resistant tuberculosis (MDR-TB), extremely drug resistant tuberculosis (XDR-TB), or totally drug resistant tuberculosis (TDR-TB) must not travel on any commercial flight, whatever the duration, under any circumstances, until they are proven to be non-infectious with two consecutive negative sputum culture results. The latest guidelines (national and/or international) should be consulted for travel restrictions regarding cases or contacts of patients with respiratory viral infections of high mortality, such as severe acute respiratory syndrome. This is especially important for outbreaks of emerging respiratory infection [14].

ASSESSMENT OF FITNESS TO FLY

To date, assessment of fitness to fly in patients with pulmonary disease has largely been studied in patients with COPD, although patients with restrictive lung disease and cystic fibrosis have also been studied. Medical history and physical examination should routinely be performed as part of a preflight screening evaluation especially amongst travelers with chronic diseases. Co-morbid conditions such as cardio and cerebrovascular disease, other neurological disease and anemia should also be evaluated. A number of methods to assess for hypoxemia risk during air travel are available, including sea-level measurement of SpO2 and PaO2, the use of equations to predict hypoxemia at altitude, and also hypoxic challenge testing. The latter, which is performed under either normobaric or hypobaric conditions, is the preferred method to assess risk of hypoxemia at altitude [33-35].

The following groups should be specifically assessed: those with severe COPD, asthma, severe restrictive lung disease, cystic fibrosis, history of air travel intolerance / respiratory symptoms during past flights ,co-morbidities worsened by hypoxemia, infectious respiratory diseases either acute or chronic especially pulmonary TB and COVID-19,recent pneumothorax; risk of or previous venous thromboembolism, and the need for ventilator support.

CONCLUSIONS

With optimized care, patients can fly without any additional risk. Clinical and functional evaluation for fitness to fly and possible risk factors for in-flight hypoxemia should be assessed in all respiratory diseases patients before flying. Many patients tolerate hypoxemia without symptoms or adverse event. However, proactive strategies to identify patients at risk and implementing preventive measures for adverse events in high-risk patients should be encouraged to achieve better disease management.

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Appendix 1. When to delay travel to avoid spreading COVID-19: adapted from the U.S. Centers for Disease Control and Prevention (https://www.cdc.gov/coronavirus/2019-ncov/travelers/when-to-delay-travel.html)

- Don't travel if you or any of your travel companions
  - Are sick
  - Have suspected or diagnosed COVID-19 (even if you don't have symptoms)
  - Have been around someone with suspected or diagnosed COVID-19 in the past 14 days (even if they did not have symptoms).
- CDC can restrict the travel of people known or believed to have COVID-19, or who have been exposed to a person with COVID-19, if they plan to travel. State, local, and territorial health departments and foreign public health authorities can also restrict travel of infected or exposed people within their jurisdictions.
- Getting trip cancellation insurance might help ensure you are able to make a last-minute cancellation or change your itinerary without losing money on flights, cruises, train tickets, or pre-paid lodgings.
- For all travel, take preventive measures to protect yourself and others, such as wearing a face mask for the duration of your trip, especially if using public transportation.