Chapter 17
Air Travel in Diffuse Cystic Lung Diseases

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Introduction

Air travel is associated with increased risk for patients with chronic lung disease. In the absence of lung disease, the body's compensatory response to the hypobaric hypoxic environment of air travel is adequate, and respiratory symptoms account for only 10–15% of in-flight medical emergencies [1]. Much of the available literature regarding the clinical assessment of a patient's fitness to fly has focused on the risk of in-flight hypoxemia [2, 3]. In addition to hypoxemia, patients with diffuse cystic lung diseases (DCLDs) may also face an increased risk of in-flight pneumothorax. In this chapter, we discuss the physiologic changes that occur with air travel and their clinical implications for patients with DCLD.

Physiologic Response to Altitude

Though the cruising altitude of commercial aircrafts may vary from 14,875 feet to 47,000 feet, the Federal Aviation Administration (FAA) regulations require that commercial aircraft cabins be pressurized to an altitude of 8000 feet or 2438 meters [4, 5]. Barometric pressure at this elevation is 565 millimeters of mercury (mmHg),

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and the partial pressure of inspired oxygen (P_IO_2) is 100–105 mmHg, which is the equivalent of breathing 15.1% oxygen at sea level. In healthy individuals, this will result in a partial pressure of arterial oxygen (P_aO_2) of 60–70 mmHg, which is generally tolerated well, as would be expected based on the oxygen-hemoglobin dissociation curve (Fig. 17.1). Beginning at an altitude of 5000 feet night vision is affected, an effect most important for pilots. Per FAA regulations, pilots must use supplemental oxygen during nocturnal flights at altitudes above 5000 feet. Other than night vision impairment, healthy individuals do not usually have any symptoms of hypoxia below 12,000 feet. Between 12,000 and 15,000 feet, various central nervous system (CNS) effects occur, including euphoria, headache, mild cognitive impairment, drowsiness, dizziness, and headache. Above 15,000 feet, cognitive function can deteriorate significantly and quickly, with a pilot's ability to operate an aircraft substantially impaired in as little as 15 min. In addition, peripheral vision becomes severely impaired (tunnel vision) at 15,000 feet, and above 20,000 feet unconsciousness can occur in as quickly as 12 min [6, 7]. From a pulmonary standpoint, the physiologic response to hypoxia is to increase alveolar ventilation, thus minimizing the reduction in alveolar PO_2. This hypoxic ventilatory response is mediated by peripheral chemoreceptors in the carotid body [8]. In extreme

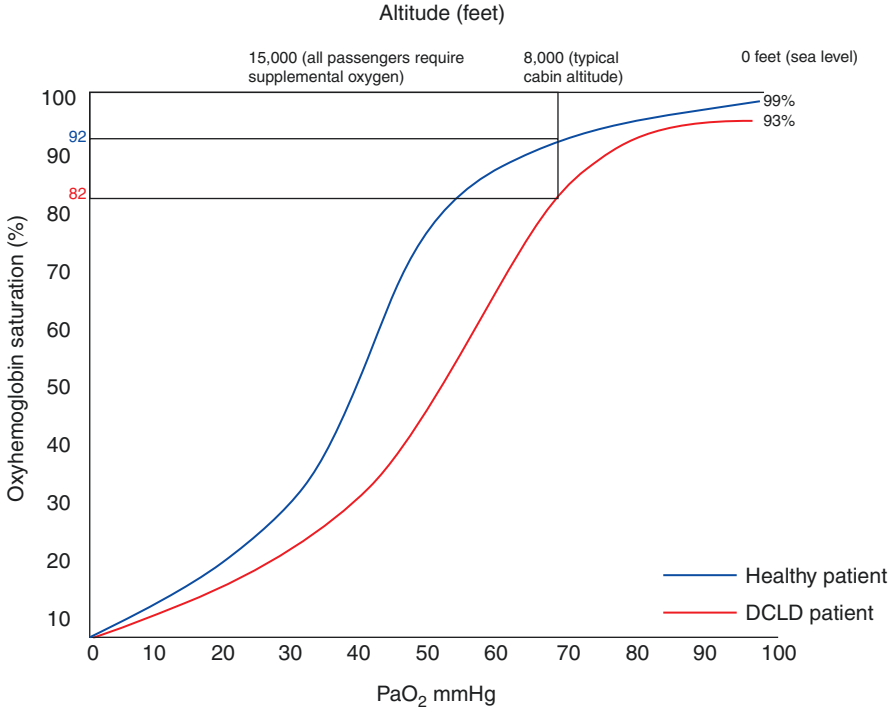

Fig. 17.1 Oxygen-hemoglobin dissociation curve for healthy individuals and patients with diffuse cystic lung disease at the equivalent altitude of a commercial airline cabin. DCLD diffuse cystic lung disease, PaO_2 arterial oxygen tension

scenarios, this response can be dramatic. For example, a study examined the arterial blood gas data from a simulated climb to the summit of Mt. Everest (through exposure to reduced PiO_2) and found the lowest $PaCO_2$ to be 9.8 mmHg. The average pH among that group was 7.53. These data demonstrate the significant hypoxic ventilatory response that could occur at high altitude, such as the hypobaric hypoxic environment of an airplane cabin [9]. In addition to the augmentation of minute ventilation mediated by the hypoxic ventilatory response, the pulmonary vasoconstriction caused by hypoxia leads to a redistribution of blood flow in the lungs in an attempt to improve ventilation-perfusion matching [10]. Finally, the diffusion of oxygen across the alveolar-capillary membrane is limited at altitude by multiple factors. The decrease in barometric pressure and consequent drop in alveolar partial pressure of oxygen (PAO_2) diminishes the pressure gradient for the diffusion of oxygen. This is especially notable with exercise, as the increase in cardiac output leads to a reduction in transit time for red blood cells through the pulmonary capillary bed, which exacerbates the diffusion impairment. Furthermore, the decreased PaO_2 at altitude lands on the steep portion of the oxygen-hemoglobin dissociation curve (see Fig. 17.1), which leads to a proportionally greater reduction in oxygen uptake [11]. Consequentially, small reductions in PaO_2 at altitude result in a significant reduction in oxygen delivery.

In the hypoxic environment at high altitude, cardiac output increases to maintain oxygen delivery to the peripheral tissues. This is mediated primarily through an increase in heart rate [12]. Stroke volume is actually decreased with exposure to altitude, possibly due to decreased LV preload as a result of the increased RV afterload from the hypoxic pulmonary vasoconstriction [13, 14]. Myocardial contractility appears to be maintained even at extreme altitude [13, 14].

The physiologic stress induced by the hypoxia of altitude is magnified in patients with underlying cardiopulmonary diseases. In certain cases, the attempts at compensation may be problematic. For example, a patient with obstructive lung disease may experience progressive expiratory flow limitation with attempts to increase minute ventilation, leading to dynamic hyperinflation and air trapping resulting in severe dyspnea. In patients with significant underlying lung disease and baseline gas exchange abnormalities, minimal exertion (e.g., ambulating to the lavatory) in the airplane could result in significant hypoxemia. For patients with cardiovascular disease, meeting the required augmentation in cardiac output may be difficult, potentially resulting in tissue hypoperfusion. Patients with pulmonary hypertension are at risk for the negative impact of hypoxia on the pulmonary vasculature and the potential increased right ventricular afterload (Fig. 17.2).

Physiologic Implications of Diving

Underwater diving results in exposure to increased pressure that is directly proportional to the depth of the dive, creating a hyperbaric environment in contrast to the hypobaric conditions encountered during air travel. This results in an increased risk

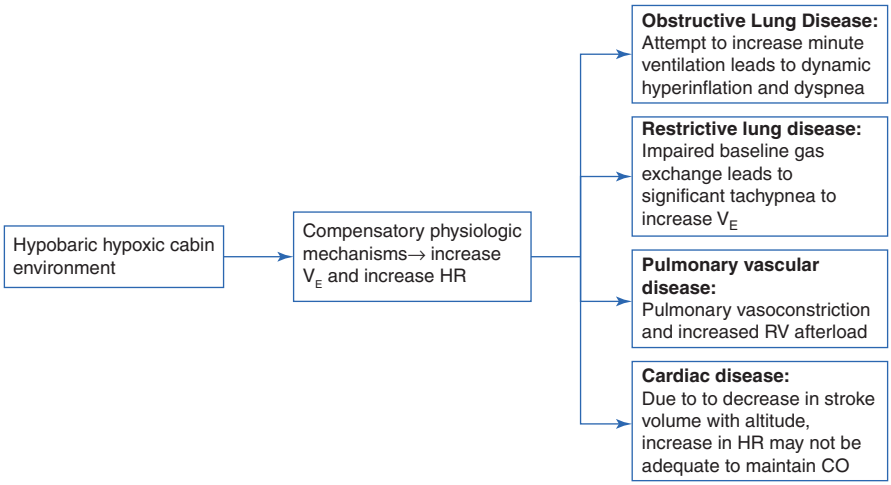

Fig. 17.2 Physiologic consequences of the hypobaric hypoxic cabin environment during commercial air travel in patients with underlying lung disease. CO cardiac output, HR heart rate, RV right ventricle, V_E minute ventilation

of pulmonary barotrauma, which could occur either during descent or ascent. For patients with DCLD, this barotrauma may manifest in the form of cyst rupture leading to a spontaneous pneumothorax. Divers breathe compressed gas that is pressurized to ambient pressure so that during descent the pressure gradients for the gas are not significantly altered. During ascent, the expansion of gas within the lungs can lead to increased transpulmonary pressures, which can lead to barotrauma. This effect is amplified by inadequate exhalation, which could be a result of breath holding or may occur because of underlying airway obstruction in patients with asthma, chronic obstructive pulmonary disease (COPD), certain DCLDs, etc. Immersion in water results in increased hydrostatic pressure, decreasing blood pooling in the peripheral circulation and therefore increasing venous return, central venous pressure, and cardiac output. Energy requirements for diving are substantial. Swimming even at slow nautical speeds requires significant oxygen consumption (VO_2). Divers with a peak $VO_2 < 20$ mL/kg/min may rapidly exceed their anaerobic threshold during a dive and develop severe dyspnea while underwater [15].

Clinical Implications

Hypoxia and Air Travel in DCLD

DCLD patients, similar to patients with other lung diseases, are at risk for worsening gas exchange during air travel due to the hypobaric hypoxic cabin environment. However, predicting the severity of in-flight hypoxia is challenging, and most

studies on this issue have focused on patients with COPD. Among DCLD patients, those with room air hypoxia or baseline long-term oxygen therapy (LTOT) requirement have the highest risk of in-flight hypoxia.

Pneumothorax and Air Travel in DCLD

The physiologic changes that occur with air travel raise a particular concern for in-flight pneumothorax in patients with DCLD. Boyle's law states that, assuming a constant temperature, the pressure and volume of a gas are inversely proportional. Therefore, as atmospheric pressure falls with air travel, gas volume expands. As noted by Baumann, this concept can be appreciated by observing a bag of potato chips during air travel – with ascent the expansion of the air in the sealed bag gives it the appearance of an inflated balloon [16].

If a parenchymal cyst has no communication with the tracheobronchial tree, significant volume expansion (up to 40%) can occur in flight [17], potentially leading to rupture of the cyst, which could cause a pneumothorax if the visceral pleura is disrupted. Postmus and colleagues postulate that variability in the size of the visceral pleural defect could affect the timing of pneumothorax development after flight. Smaller defects may result in the slow accumulation of air in the pleural space leading to a delayed presentation of pneumothorax. Furthermore, small defects may be asymptomatic and spontaneously seal. There have been some reports of patients with DCLD developing pneumothoraces several days after air travel, suggesting the possibility of this delayed presentation [18], although it is possible that these represent incidental events in a population enriched for spontaneous pneumothoraces, and are entirely unrelated to the air travel.

While the risk of hypoxia with air travel has been extensively addressed in the literature, there is comparatively little data available with respect to pneumothorax. The incidence of in-flight pneumothorax in the general population appears to be extremely low. A prospective multicenter observational study examining air travel outcomes for patients with lung disease found symptoms of in-flight respiratory distress reported by 18% of patients, but there were no in-flight pneumothoraces [19, 20]. In a retrospective analysis of 10,189 cases of in-flight medical emergencies on two European airlines, Sand and colleagues found no cases of pneumothorax [21]. Additionally, neither an analysis of 11,920 medical emergencies on multiple commercial airlines nor a recent systematic review of in-flight medical emergencies mentioned any cases of pneumothorax [22, 23]. However, given the physiologic possibility of cyst expansion during air travel, there is clinical concern for an increased risk of in-flight pneumothorax in patients with DCLD, and clinicians often are asked to provide counseling in this area. Although the data on the risk of development of spontaneous pneumothorax associated with air travel remain relatively sparse, there have been some studies examining the risk of pneumothorax with air travel in patients with certain DCLDs.

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is a rare DCLD characterized by infiltration of the lung parenchyma with abnormal smooth muscle-like cells harboring mutations in the Tuberous Sclerosis Complex genes. This disease occurs almost exclusively in women, and it tends to be worse in premenopausal women as compared to postmenopausal women [24]. LAM is associated with a high risk of spontaneous pneumothorax, with 55–73% of patients experiencing at least one episode of pneumothorax in their lifetime [25]. Several studies have examined the issue of air travel–associated spontaneous pneumothorax in patients with LAM.

Pollock-BarZiv and colleagues surveyed LAM patients in the United States and the United Kingdom to ascertain the risk of air travel–associated spontaneous pneumothorax. Of the 276 women with LAM who had ever flown for a total of 454 flights, 10 women reported experiencing an air travel–related spontaneous pneumothorax, equating to a per-flight pneumothorax risk of 2.2%. However, in five of these patients, the symptoms of pneumothorax were present prior to boarding the plane, thus suggesting the pneumothorax occurred prior to initiation of air travel and that the actual risk of air travel–related pneumothorax in LAM may be closer to ~1% as compared to ~2% [26].

In another study, LAM patients traveling to the National Institutes of Health were assessed for the presence of pneumothorax at arrival to the center. Similar estimates were also generated for patients traveling to the NIH with other interstitial lung diseases such as idiopathic pulmonary fibrosis and sarcoidosis. A total of 281 LAM patients were evaluated in this study, and 16 arrived with a radiographically documented pneumothorax. In contrast, none of the patients with idiopathic pulmonary fibrosis or sarcoidosis had radiographic evidence of pneumothorax on arrival. In 9 out of the 16 LAM patients, the pneumothorax had preceded the study visit. From the remaining 7 patients, the authors estimated that the per-flight risk of air travel–related spontaneous pneumothorax in LAM is ~1%, and that the presence of pneumothorax after travel may be more related to the baseline increased risk of pneumothorax in LAM as opposed to a true travel-related increase in risk. Patients with reduced FEV1 and larger cysts on chest CT scans may be at higher risk of developing air travel–related spontaneous pneumothorax [27].

In the most recent study evaluating the relationship between air travel and risk of pneumothorax in LAM, Gonano and colleagues conducted a survey-based assessment of 145 LAM patients across multiple countries in the European Union and the United Kingdom. The authors calculated an estimate of ~3% per-flight risk of development of spontaneous pneumothorax in patients with LAM. Notable difference in this study as compared to the prior investigations is that any pneumothorax occurring within 30 days following air travel was considered to be related to air travel, thus likely leading to an over-estimation of the risk [28].

Birt-Hogg-Dubé Syndrome

Birt-Hogg-Dubé (BHD) syndrome is a rare autosomal dominant disorder caused by a germline mutation in the folliculin (*FLCN*) gene. BHD results in the development of hair follicle tumors (fibrofolliculomas), pulmonary cysts, and renal neoplasms. Lung cysts are usually lentiform and have a basilar distribution. The risk of spontaneous pneumothorax in BHD is approximately 50 times greater than the general population after adjusting for age [29]. In a retrospective survey-based analysis of 145 BHD patients who had flown at least once in their lifetime, Johannesma and colleagues estimated the risk of air travel and scuba diving–related spontaneous pneumothorax to be 0.63% and 0.33%, respectively. The risk of air travel–related pneumothorax was proportional to the number of cysts on chest CT [30]. In another survey-based assessment of 104 BHD patients recruited from the Rare Lung Diseases Clinic Network and the BHD Foundation, Gupta et al. estimated the air travel–related pneumothorax risk at 0.12 events per 100 flights (0.1%) [31].

Pulmonary Langerhans Cell Histiocytosis

Pulmonary Langerhans cell histiocytosis (PLCH) is a DCLD that results from the peribronchiolar accumulation of dendritic cells harboring activating mutations in the mitogen-activating protein kinase pathway, and it is strongly associated with exposure to cigarette smoke [32]. Spontaneous pneumothorax occurs in approximately 15–20% of patients with PLCH (27). In a recently published study, Singla and colleagues performed a survey-based assessment of 94 patients with PLCH. Eighty-two subjects had flown at least once in their lifetime for an estimated total of 742 flights. Two patients experienced an in-flight pneumothorax, amounting to an air travel–related pneumothorax risk of 0.27 per 100 flights (~0.3%). Individual-level risk factors that could portend a higher risk of air travel–related pneumothorax were not determined in this analysis owing to the lack of chest CT and pulmonary function test data on the subjects [33].

Air Travel Following an Episode of Spontaneous Pneumothorax

There is a paucity of evidence regarding when patients can safely undertake air travel following an episode of spontaneous pneumothorax. We follow the recommendations put forth by the British Thoracic Society and the International Air Transport Association, which suggest that air travel be delayed for 7 days following radiographic resolution of a spontaneous pneumothorax and 14 days following radiographic resolution of a traumatic pneumothorax [34, 35]. This duration may be shorter in patients who can travel with a Heimlich valve chest tube [36].

Summary of Air Travel–Related Spontaneous Pneumothorax in DCLDs

In general, the risk of spontaneous pneumothorax associated with air travel for patients with LAM, BHD, and PLCH appears to be low (~1 episode of spontaneous pneumothorax per 100 flights). Disease-specific risk of spontaneous pneumothorax with other DCLDs has not been estimated; however, it is likely that the risk is similar to the abovementioned estimates seen in the three major DCLDs. In general, the risk of pneumothorax with air travel should not be considered prohibitive for most DCLD patients, except perhaps for those with very limited respiratory reserves. The risks should be discussed in a pre-flight clinical assessment, which should also include counseling on concerning symptoms that might prompt a medical evaluation prior to undertaking air travel (Table 17.1).

Diving Risk and DCLD

Although there are no reports of diving-related complications in patients with DCLDs, there is the possibility of cyst rupture associated with pressure changes that could lead to the development of barotrauma complications such as pneumothorax and pneumomediastinum with ascent. Such complications due to barotrauma during a dive could be fatal, and management of a pneumothorax could be difficult at a remote diving site. As such, we recommend that patients with DCLD not attempt underwater diving.

Table 17.1 Checklist of items for pre-flight assessment of DCLD patients

Educate patients about the signs and symptoms of spontaneous pneumothorax such as sudden onset shortness of breath and pleuritic chest pain
Counsel patients to seek medical evaluation and not board the plane if they experience symptoms suggestive of pneumothorax prior to air travel
Reassure patients that the overall risk of air travel–related pneumothorax is low (~1 per 100 flights) and that majority of the DCLD patients are able to fly safely
Consider individualizing the counseling regarding pneumothorax and air travel based on patient's underlying disease severity taking into account the following risk factors: age and overall functional status, cardiopulmonary reserve to tolerate a pneumothorax, pulmonary function tests, number and size of cysts on chest CT scan, prior history of pneumothorax, and prior pleurodesis
Suggest patients wait for 7 days following radiographic resolution of a spontaneous pneumothorax prior to undertaking air travel
Assess patients for the need for in-flight supplemental oxygen as per the algorithm in Fig. 17.3

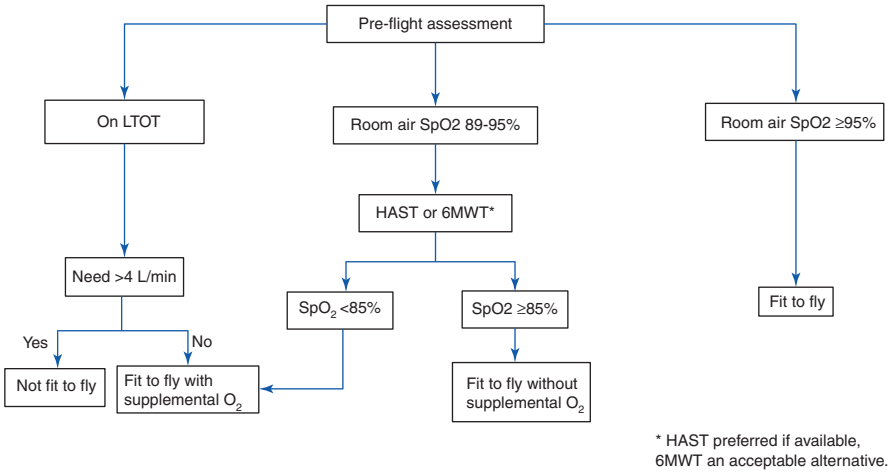

Fig. 17.3 Algorithm for the assessment of oxygenation and fitness to fly in patients with diffuse cystic lung diseases. * If available, HAST is preferred, but 6MWT is a reasonable substitute given the limited availability of HAST. 6MWT six-minute walk test, HAST hypoxia-altitude simulation test, LTOT long-term oxygen therapy

Fitness to Fly in DCLD

Most of the medical literature examining the fitness of patients with pulmonary disease to tolerate commercial air travel is derived from patients with COPD and is focused on evaluating the risk for in-flight hypoxemia. The first step in this evaluation is room air pulse oximetry. In general, if the room air SpO2 is ≥95%, the risk of in-flight hypoxia is low, and further evaluation is not generally indicated [2]. In a study examining the effect of exposure to 15% supplemental oxygen on peripheral oxygen saturation, there no was no decrease in SpO_2 to <90% during hypoxic exposure in patients who had a sea-level SpO_2 of >95% [37]. If the oxygen saturation is <95% on room air, further evaluation is needed. Pre-flight arterial blood gas analysis can sometimes be helpful, though for practical reasons pulse oximetry is more commonly used. A sea-level room air $PaO_2 \geq 70$ mmHg is the threshold used by the Aerospace Medical Association to determine fitness to fly without the need for supplemental oxygen [38]. Similar to room air SpO_2, the predictive power of room air PaO_2 for in-flight PaO_2 is questionable, though it has had good correlation with PaO_2 during the hypoxia-altitude simulation test (HAST) in some studies [2, 3].

Consideration of the patient's overall risk is an important part of the pre-flight assessment, as the correlation between room air pulse oximetry and in-flight desaturation has not been consistent in the literature [19]. For example, patients with

impaired physiologic measurements (spirometry, diffusing capacity) or severe functional limitations may warrant further pre-flight investigation even if their room air SpO_2 is ≥95%.

For patients with a room air SpO_2 less than 95% or significant overall risk, HAST can be considered. A hypobaric hypoxic challenge test would be ideal when assessing fitness to fly, as this would most closely simulate the cabin environment. However, this is not practical clinically as hypobaric simulation capabilities are not widely available. Therefore, the normobaric HAST originally described by Gong and colleagues remains the standard and simulates the hypoxic environment of altitude using 15% oxygen in nitrogen, which approximates the FiO_2 at 8000 feet. HAST is performed by having the patient breathe 15% FiO_2 for 20 min or until a steady state is reached, defined as SpO_2 within ±2% for at least 2 min. If the SpO_2 falls below 85% during the test, the subject would likely benefit from supplemental in-flight oxygen [17, 39]. If a patient does drop below 85% during the test, then supplemental oxygen can be administered by nasal cannula and titrated during the test, and it is typically titrated to achieve $SpO_2 \geq 90\%$ [40]. If supplemental oxygen titration is not available and the patient drops below 85% on HAST, then the British Thoracic Society Guidelines recommend prescribing supplemental oxygen at 2 L/min for in-flight use [17].

There is emerging evidence to suggest that the 6-min walk test (6MWT) may be a useful surrogate of HAST for pre-flight evaluation. The utility of 6MWT to conduct functional and physiologic assessment in lung disease is well established and has particular prognostic implications in certain diffuse parenchymal lung diseases. HAST is not as widely available as the 6MWT, and given the pragmatic and logistical challenges of routine HAST administration, 6MWT may be considered a reasonable substitute during the pre-flight assessment of patients with DCLD. Chetta et al. found that desaturation during 6MWT correlated with hypoxemia during HAST [41]. In a study by Edvardsen and colleagues, in subjects with a room air SpO_2 92–95%, oxygen saturation during 6MWT showed good predictive value for in-flight desaturation (area under curve 0.8). In this study, the optimal cut-off value for predicting in-flight desaturation appeared to be $SpO_2 < 84\%$ [3]. In contrast, 6-min walk distance and forced expiratory volume in 1 s (FEV_1) had weak correlation with in-flight hypoxemia.

In general, for patients who are not on LTOT but are determined after evaluation to require supplemental O_2 during air travel, most clinicians will prescribe 2 L/min if titration during testing is not available. For patients on LTOT, many clinicians will double their flow rate for air travel (e.g., increasing to 4 L/min from baseline requirement of 2 L/min). Guidelines suggest an increase in flow rate by 1–2 L/min for patients on LTOT may be sufficient [17].

As with all patients with lung disease, the severity of their physiologic impairment should be taken into consideration while making decisions regarding air travel. If their cardiopulmonary reserve is so poor that they would develop severe acute

respiratory failure with a symptomatic pneumothorax, then the risk of flying is likely prohibitive. Also, if their baseline supplemental oxygen requirement at rest is ≥4 L/min, oxygen concentrators may not be reliably able to deliver an acceptable oxygen concentration to render flying safe, and such patients should be considered unfit to fly. Unique considerations for DCLD patients include their individual risk for pneumothorax, which is likely influenced by their specific disease process and the underlying degree of cyst profusion. Additionally, whether they have previously had pleurodesis should be considered. Our approach to the pre-flight assessment of patients with DCLD includes the checklist in Table 17.1 as well as the algorithm illustrated in Fig. 17.3.

Conclusion

Evaluation of fitness to fly in patients with DCLD is complex. In addition to the concerns regarding in-flight hypoxemia, DCLD patients must be assessed for their risk for pneumothorax. Insights from recent studies regarding the risk of in-flight pneumothorax provide some guidance for clinicians. In general, the risk of air travel–related spontaneous pneumothorax is low, and most patients with DCLDs should be able to undertake air travel safely. Adjunctive physiologic testing (6MWT, HAST) is helpful for evaluating the risk of in-flight hypoxemia. An overall risk assessment of individual DCLD patients remains a crucial step in the pre-flight work-up. A checklist is presented for the pre-flight assessment of DCLD patients that integrates the risk of in-flight pneumothorax and hypoxemia.

Key Learning Points

- Pre-flight safety assessment of patients with DCLDs requires consideration of the risk for in-flight hypoxemia as well as the potential to develop spontaneous pneumothorax.
- The risk of air travel–related spontaneous pneumothorax is approximately 1 event per 100 flights in patients with DCLDs, and it is not prohibitive for majority of the patients.
- DCLD patients should be educated about the signs and symptoms of spontaneous pneumothorax and counseled to not board the plane if they experience these symptoms prior to boarding.
- Assessment of resting and exercise pulse oximetry may be a reasonable substitute for high-altitude simulation test for assessment of the need for in-flight supplemental oxygen.
- DCLD patients should be counseled to avoid scuba diving.

Conflicts of Interest The authors declare no conflicts of interest.

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