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AIR TRAVEL: IMPLICATIONS FOR PATIENTS WITH PULMONARY DISEASES

INTRODUCTION

Air travel is now a common mode of travel for millions. It is estimated that over one billion passengers travel by air world-wide each year. Although aircraft cabins are pressurized, they are not pressurized to sea-level and aircraft cabin altitude can thus approach 2438 metres (8000 feet) while the aircraft is flying at 11,582 m (38,000 ft). Thus, a hypobaric environment exists in aircraft cruising at an altitude. At an altitude of 8000 ft, partial pressure of oxygen falls to a level, equivalent to breathing oxygen at FiO_2 of 15.1%. In a healthy individual, PaO_2 falls to 53-64 mm Hg and SpO_2 falls to 85-91%, which one can tolerate.

In patients with respiratory diseases, hypobaric environment would lead to worsening of blood gases particularly in those with borderline values at ground level. 5% of commercial airline passengers were ambulatory patients with some illness including COPD. It is estimated that approximately 10% of in-flight medical emergencies calls are respiratory in nature. Respiratory in-flight emergencies are the third most common cause for diversion of air craft and account for approximately 17% of such diversions. This signifies the importance of evaluation of patients with pulmonary diseases.

Apart from risk of worsening of symptoms of chronic respiratory diseases, other important aspects pertaining to air travel are risk of spread of infectious diseases in-flight and risk of deep venous thrombosis (DVT).

Chronic respiratory diseases

Patients of severe COPD or asthma, severe restrictive lung diseases, cystic fibrosis, recent pneumothorax, patients with pre-existing requirement for oxygen or ventilatory support, patients with history of air travel intolerance with respiratory symptoms (dyspnea, chest pain, confusion or syncope) and patients with conditions worsened by hypoxemia (cerebro vascular disease, coronary artery disease, heart failure) should undergo pre-flight evaluation.

PREFLIGHT EVALUATION

The main aim of preflight evaluation is to pick up those individuals from high risk population, who are likely to develop hypoxemia ($\text{PaO}_2 < 50$ mm Hg) at an altitude of 8000 ft. Detailed history & examination, spirometry, pulse oximetry, arterial blood gases (ABG), regression estimates of PaO_2 and Hypoxia Inhalation Test (HIT) constitute the various components of preflight evaluation. There are recommendations but no guidelines currently available on preflight evaluation. In the following few passages we would dwell upon the available evidence for each of these tests and logical application of them.

Estimation of PaO_2 at altitude

PaO_2 of 68 or 72 mm Hg at ground level predicts an in-cabin PaO_2 of 50 and 55 mm Hg respectively, assuming constant alveolar-arterial (A-a) gradient. PaO_2 at sea level alone as a predictor may misclassify many patients as the A-a gradient and $\text{PaO}_2/\text{FiO}_2$ ratios do not remain constant at altitudes. Various regression equations for estimating PaO_2 at altitude have been derived from studies, which exposed patients to hypoxic and hypobaric situations. (Box 1)

Box 1

$20.38 - (3 \times \text{Altitude in thousands of feet}) + 0.67 \times \text{PaO}_2 \text{ Ground}$
 $22.8 - (2.74 \times \text{Altitude}) + 0.68 \times \text{PaO}_2 \text{ Ground (mmHg)}$
 $0.410 \times \text{PaO}_2 \text{ Ground (mmHg)} + 17.652$
 $0.519 \times \text{PaO}_2 \text{ Ground (mmHg)} + 11.855 \times \text{FEV1 (liters)} - 1.760$
 $0.453 \times \text{PaO}_2 \text{ Ground (mmHg)} + 0.386 \times (\text{FEV1\% pred}) + 2.44$
 $0.294 \times \text{PaO}_2 \text{ Ground (mmHg)} + 0.086(\text{FEV1\%}) + 23.211$
 $0.245 \times \text{PaO}_2 \text{ Ground (mmHg)} + 0.171(\text{FEV1/FVC\%}) + 21.028$
 $0.228 \times \text{PaO}_2 \text{ Ground (mmHg)} + 20.098(\text{FEV1/FVC}) + 22.258$

Formulae considering spirometric values generally have better prediction compared to formulae considering only blood gases at ground level. But addition of more than one spirometric value generally does not increase the accuracy.

If the predicted PaO_2 is 50 ± 3 mm Hg, then one is advised to perform HIT. Hypoxia Inhalation Test (HIT).

Hypoxia Inhalation Test (HIT)

During this test patients are exposed to 15.1% oxygen, simulating FiO_2 of aircraft cabin at 8000 ft altitude. This can be achieved by breathing 15.1% oxygen by face mask, or by breathing in a body box with FiO_2 of 15.1% or breathing 30-35% nitrogen by venturi mask. Although this reduces FiO_2 , flight environment and duration are not created. Patients showing hypoxia $\text{PaO}_2 < 50$ mm Hg are candidates for in-flight supplemental oxygen.

Pulse oximetry

Although there are no studies validating the utility of pulse oximetry, British Thoracic Society (BTS) recommendations state that, pulse oximetry could be used as first test for preflight evaluation. Use of pulse oximetry for self monitoring of SpO_2 during flight is not encouraged. The following flow chart (figure 1) summarizes the BTS recommendations.

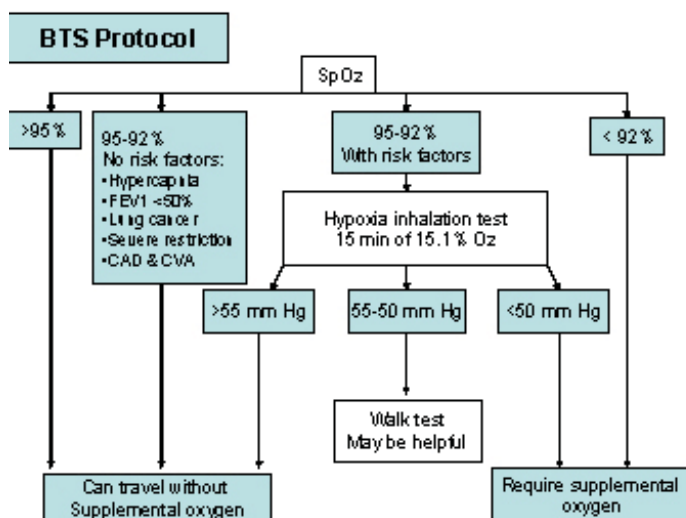


Figure 1: BTS recommendations

TRAVEL ADVICE

All patients are given the following advice:

- Carry well-filled reliever and preventer inhalers in their hand luggage
- Portable battery-operated nebulisers may be used
- Spacers are as effective as nebulisers
- A full supply of all medication should be taken as hand luggage, preferably in the original packaging with pharmacy labels.

Patients who require supplemental oxygen should receive 2–4 liters/min, preferably through nasal prongs. In-flight oxygen need not be switched on until the plane is at cruising altitude, and may be switched off at the start of descent. For patients on oxygen at sea level, the rate should only be increased while at cruising altitude.

Pneumothorax

The volume of gas in a non-communicating bulla/cavity will increase by 37.6% on ascent from sea level to 2438m (8000ft). Gas expansion with altitude is significantly greater than predicted by Boyle's law as applied to dry gas alone. This puts patients of pneumothorax at risk for worsening of symptoms during air travel. Patients with untreated pneumothorax should not travel by flight. Patients of pneumothorax treated with medical methods can travel after 1 week but those treated with surgical methods can travel as soon as they recover from surgery.

Deep vein thrombosis (DVT)

Air travel is considered a risk factor for DVT. Possible hypotheses for this include restricted mobility, seated position, dehydration and

alcohol ingestion, compression of popliteal veins against seat edge and altered balance between pro-thrombotic and pro-fibrinolytic systems at hypobaric, hypoxic environment in aircraft. BTS recommendations, stratify passengers into 4 risk groups and advice accordingly. (Table 1)

Risk status	Risk factors	Advice
All passengers	Low	<ul style="list-style-type: none"> • Avoid excess alcohol and caffeine-containing drinks • Remain mobile / exercise legs
Slightly increased	Aged over 40 Extensive varicose veins Polycythemia Within 72 hours of minor surgery	<ul style="list-style-type: none"> • Above plus consider: • Take short periods of sleep • Consider support hosiery
Moderately increased	Family history of VTE Recent MI Pregnancy or early post-natal Oestrogen therapy Limb trauma or paralysis	<ul style="list-style-type: none"> • Above plus consider: • Pre-flight aspirin • Graduating compression stockings
High risk	Previous VTE Thrombophilia Within six weeks of major surgery Previous stroke Current malignancy	<ul style="list-style-type: none"> • Avoid flying or recommend low molecular weight heparin or formal anticoagulation (including return journey)

Table 1 : BTS recommendations for prevention of DVT

SPREAD OF INFECTIOUS DISEASES

Epidemiological studies suggest respiratory diseases like tuberculosis, measles and influenza could spread during travel by flight

Tuberculosis

Air flow in aircraft is laminar. This limits spread of infection from an infectious patient to those sitting in few rows in front and behind. Crew exposed to patients for prolonged periods (more than 10-11 hrs) are at risk of infection. Although epidemiological studies show risk of infection, till date there is no case of disease developing after exposure in-flight. WHO states that air travel does not carry a greater risk of infection with M. tuberculosis than traveling by rail, bus or attending conferences.

WHO guidelines state that, HIV negative patients who have completed two weeks of effective anti tuberculous treatment and HIV positive patients three smear negative sputum examinations on separate days or a single negative sputum culture can travel in commercial aircraft.

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EXHALED BIOMARKERS IN RESPIRATORY DISEASE

INTRODUCTION

Clinicians at the present time make a diagnosis of asthma or COPD based on a patient's clinical history, physical signs, pulmonary function tests, arterial blood gas analysis and radiology. None of these methods of reaching a clinical diagnosis actually measure the degree of inflammation in the respiratory tract. In a sense, we never directly use a measure of inflammation to reach a diagnosis or monitor therapy.

Biomarkers are objectively measured and

evaluated indicators of biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention. We can measure the gases in expired air, substances present in expiratory breath condensate, the pH of this sample. The temperature of the expelled air can be recorded.

It is easy to see why this has been viewed as such an exciting development for respiratory medicine. A large proportion of respiratory diseases are the result of inflammation. Examples

are asthma, COPD, ILD, bronchiectasis and cystic fibrosis. Measuring biomarkers may make it possible to quantify airway inflammation in the future. This should help to arrive at a diagnosis and then to titrate appropriate treatment.

For a moment, let us consider the alternatives available to us currently to measure inflammation in a disease like asthma. Airway biopsies can be done and are indeed the gold standard. The procedure is invasive and cannot be repeated often or at every office visit. It is not feasible in the elderly or in very young children. Bronchoalveolar lavage is a possibility but is equally invasive and can transiently impair gas exchange and be responsible for the spread of infection.

The patient's symptoms are also not an ideal measure of disease severity as patients differ in their perception of dyspnea. Wheeze is relieved by bronchodilators which therefore mask true disease severity. The histamine challenge test is also confounded by short and long acting beta agonist (SABA/LABA) use and cannot be used for follow up repeatedly.

Last but not least, sputum induction is a possibility but is unpleasant and causes inflammation which can last up to 24 hours.

EXHALED BREATH CONDENSATE (EBC)

The epithelial lining fluid contains up to 200 different volatile and non-volatile substances. Initial studies focused on volatile substances particularly nitric oxide (NO). The current emphasis seems to be on non-volatile substances especially proteins, lipids, oxidants and nucleotides. This theoretically seems to be an excellent means of determining the nature and degree of host inflammatory responses in the lung. The possibility that this investigation could become a point-of-care real-time analysis tool in the near future is being looked at with great interest.

Collection of EBC

Exhaled air is saturated with water vapor which

can be condensed with cooling. Aerosol particles from the lower tract are also present. It has been determined that some constituents are from the airway while others come primarily from the alveoli. Airway constituents like hydrogen peroxide are flow dependent.

A glass, polystyrene or polypropylene container immersed in an ice-bucket like outer casing is used. Cooling can be with ice, dry ice or liquid nitrogen. Nose clips are recommended by some but can cause the nasopharyngeal velum to open and may cause contamination with nasal secretions. It takes 5-10 minutes of breathing at tidal volumes for an adult to collect 1-3 ml of EBC.

Contamination may be from rebreathing exhaled air and also from saliva. The former can be avoided using non rebreathing valves in the tube while the latter can be prevented by saliva traps and rinsing the mouth prior to the procedure. Any salivary contamination that does occur can be quantified using amylase measurements

Inflammatory mediators

A variety of mediators have been detected in various respiratory conditions. In smokers hydrogen peroxide levels and 8-isoprostane levels have been studied. In COPD various cytokines and serotonin levels have been looked at. Similarly in asthma a whole host of inflammatory mediators have been identified. Leukotriene levels have been researched in chronic bronchitis. Peroxide, 8-isoprostane, and prostaglandin E2 have been studied in ARDS/ALI patients.

APPLICATIONS OF EXHALED BIOMARKERS

Smoking

Hydrogen peroxide is a marker of oxidant activity. Levels in smokers are approximately five times higher than in non-smokers. Male smokers tend to have higher levels than female smokers. Levels in the EBC are lower than those found in

the alveoli because the anti-oxidant system tends to remove some part of the peroxide generated. Higher levels may therefore indicate an inability to remove peroxide in that particular individual and may be an indication that there is greater susceptibility to smoking related disorders in the future.

Asthma

It was first shown by Alving et al in 1993 that NO levels are increased in bronchial asthma. In pathological situations, it is a pro-inflammatory substance with immuno-modulatory effects. It predisposes to the development of hyper-reactivity of the airway. Paradoxically, in the physiological situation it actually relaxes smooth muscle. It originates primarily in the airway epithelium.

Levels of NO may rise in a wide variety of conditions, but the rise is most marked in allergic airway disease. It is easily measured by portable, inexpensive meters. It probably is a more relevant measure of airway inflammation which complements spirometry. It is known that levels correlate well with the degree of eosinophilic inflammation in the airway. It is also a fact that eosinophilic inflammation is highly steroid responsive. Therefore raised levels in individuals with non-specific symptoms can effectively predict steroid responsiveness. The use of inhaled steroids results in a dose dependent fall in NO levels. NO levels can effectively differentiate asthma from non-asthma. It can pick up disease where lung function is still normal and spirometry does not reveal any abnormality. Eosinophilic bronchitis, cough-variant asthma and post-viral hyper-responsiveness are other conditions where raised levels predict steroid responsiveness. In contrast, in conditions like vocal cord dysfunction or COPD, levels are unlikely to be significantly raised and therefore a response to ICS cannot be expected.

No measurements in wheezy infants can help differentiate asthma from non-asthma and can help a decision on early institution of inhaled ICS.

Evidence for its use as a population screening tool is mixed.

Atopic individuals are known to have higher levels of NO. It complements skin testing and correlates well with IgE levels. However, there is no evidence for treatment of asymptomatic individuals at the present time.

In chronic asthma, levels can help predict exacerbations even before symptoms occur. The outcomes of ICS withdrawal can be accurately forecast. Serial measurements may allow for optimization of the ICS dose.

Peroxide levels and TBAR levels are raised in asthma. There is good correlation between the two and also with FEV1. They are suppressed with ICS use and remain suppressed for up to two weeks after discontinuation.

Nitrotyrosine is a stable end product of peroxynitrite. Increased levels are found in asthmatics that are not on steroids even in mild disease. Isoprostanes, compounds formed by peroxidation of membrane phospholipids during oxidative stress, are elevated in asthma. The correlation with spirometric values is not good though. Leukotrienes are responsible for airway smooth muscle contraction, microvascular leakage, and mucus hypersecretion. Increased levels are found in asthma with poor correlation with spirometry.

It is said that pH measurements decline by a factor of at least two logs during acute asthma. This increase in acidity is rapidly corrected with steroid intake. It has been suggested that serial values can be used for follow up. Poor reproducibility hampers its routine use.

What is the future role for EBC in asthma? It is seen that some markers persist despite ICS use. The leukotrienes are not suppressed despite ICS use. Elevated levels may be used as rationale for initiating therapy with specific inhibitors. A lack of

good correlation with spirometric values should not preclude the use of EBC results. Greater utility is likely if markers rise well before physiological changes become apparent. That would make it possible to predict an exacerbation and begin treatment before it actually occurs.

COPD

Chronic inflammation in COPD is present throughout the airways, parenchyma and pulmonary vasculature. Macrophages, T-lymphocytes (CD8+) and neutrophils are present. Tissue eosinophils are present but unlike asthma are not degranulated.

Gases that have been measured include NO, carbon monoxide (CO) and ethane. NO is not a good marker of disease severity in COPD. Its levels are increased in two subsets - those with an asthmatic component to their disease and those experiencing exacerbations. Smoking reduces levels and therefore confounds the picture.

CO levels are also increased in asthma. Environmental levels can cause variable measurements. Smoking confounds measured values. This also is not of practical value in COPD.

Isoprostanes are increased in smokers, asthma, and even in those with ILD. Measurements do not help guide therapy in COPD. The NO metabolites are also increased in asthma, smokers and therefore also are not practical. TBARs (thiobarbituric acid reactive substances) are formed by lipid peroxidation. Levels are undetectable in healthy non-smokers. Levels are higher in stable COPD with no reference to current smoking status.

ADVANTAGES AND LIMITATIONS OF EBC

EBC may in the future provide a simple, point-of-care intervention. It is not an intrusive or invasive investigation and can be done in the very young and in those who are sick. This includes those on a ventilator. Domiciliary measurements are likely

to be possible for at least some of the markers. Drug dosage could possibly be tailored to EBC values especially ICS. At the present time the main disadvantage of EBC is lack of standardization of breath sampling methods. There is also the inability to pin point with precision where exactly a marker originates (e.g. airway or alveolus). Concentration artifacts confound sampling. Markers other than those resulting from oxidative stress have not been extensively tested. There is little information about markers for ILD at present.

CONCLUSIONS

Biomarkers may at some time in the future become a useful non-invasive adjunct in the diagnosis and follow up of patients with pulmonary disease. Further work is needed to standardize, validate and better define the clinical utility of this emerging technique.

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Journal Club Critique

Nahid P, Gonzalez LC, Rudoy I, de Jong BC, Unger A, Kawamura LM, et al.
Treatment Outcomes of Patients with HIV and Tuberculosis.
Am J Respir Crit Care Med 2007; 175: 1199-1206.

Summary:

This study was aimed at evaluating the outcome of treatment for tuberculosis (TB) in HIV infected patients after stratification by the duration of rifampicin (or other rifamycins) based anti tuberculosis therapy (ATT). A retrospective review of data on all patients with TB reporting to a Tuberculosis Control Program over a 11 year period showed that of the 700 patients, 264 (38%) were HIV infected, 315 (45%) were not infected, and 121 (17%) were not tested. Mean duration of ATT was extended to 10.2 months for HIV-infected patients versus 8.4 months for uninfected/unknown patients ($p < 0.001$). Seventeen percent of the HIV infected and 37% of the HIV uninfected/unknown patients received 6 months of rifamycin-based ATT. The relapse rate among HIV infected was 9.3 per 100 person-years versus 1.0 in HIV-uninfected/unknown patients ($p < 0.001$). HIV-infected individuals who received a standard 6-month rifamycin-based ATT regimen were more likely to relapse than those treated longer (adjusted hazard ratio, 4.33; $p = 0.02$). HIV-infected individuals who received intermittent therapy were also more likely to relapse than those treated on daily basis (adjusted hazard ratio, 4.12; $p = 0.04$). The use of highly active antiretroviral therapy (HAART) was associated with more rapid conversion of smears and cultures and with improved survival. The authors' concluded that since HIV-infected patients who received a 6-month rifamycin based ATT course and who received intermittent therapy had a higher relapse rate than HIV-infected subjects who received longer therapy or daily therapy respectively, standard 6-month ATT may be insufficient to prevent relapse in patients with HIV.

Comment:

National tuberculosis programs recommend using the same 6 month short-course intermittent ATT regimen in both HIV-infected and uninfected patients and this is a practical and attractive option for resource-limited areas. Indeed even in the current study, time period for sputum smears and cultures to become negative were similar in the HIV infected and uninfected groups and so was the percentage of patients who had conversion to negative cultures within 8 weeks of ATT. However, relapse rates, incidence of acquired drug resistance and adverse reactions to drugs administered were all significantly higher in HIV infected patients. These can be attributed to both a high prevalence of malabsorption of rifamycins and other anti tubercular drugs in HIV infected individuals as well as interactions of anti tubercular drugs with drugs used as part of HAART and other drugs administered concomitantly. In view of the high burden of HIV-TB cases annually as well as emergence of extensively drug-resistant TB (XDR-TB), even a low rate of acquired rifamycin resistance can be associated with far reaching consequences and this is why the results of this study may have important implications for management of TB in the setting of HIV infection. A higher percentage of HIV infected patients required hospitalization for tuberculosis (64.0% vs 44.3; $p < 0.001$) although hospitalization per se was not a predictor of relapse in multivariate models and this probably is an indicator of the severity of disease in them as well as their net state of immunosuppression. Thus, even though the retrospective nature of this study is its limitation, it provides an impetus for carrying out further studies to determine the optimal duration and nature of ATT in the setting of HIV infection.

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IMPORTANT DATES TO REMEMBER

Early Registration	August 31, 2007
Last date for pre-Registration	October 31, 2007
Last date for PG Workshop Registration	October 7, 2007
Last date for submission of Abstracts	July 31, 2007
Last date for withdrawal of Abstracts	October 1, 2007

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