More about... Pulmonology

Air travel and COPD

L P KRIGE, ***MB BCh, DOH, FCP (SA)***
Private practitioner, Greenacres Hospital, Port Elizabeth

Air travel increases markedly every year – it was predicted that by 2008 more than 2 billion people would have travelled by commercial airliner worldwide.[1]

A proportion of them have chronic obstructive pulmonary disease (COPD) of varying severity, some of whom may experience significant psychological and physiological stress owing to hypoxia while flying.

It is a concern, particularly in COPD patients who live at the coast where the PO_2 is high, whether they will be compromised when the PO_2 diminishes. Commercial aircraft travel between 10 000 m and 13 500 m. However, Federal Aviation Administration requirements specify that the partial pressure in an aircraft should not be less than the partial pressure at an altitude of 2 540 m.[2] The Gauteng region is about 1 600 m above sea level; therefore the cabin pressure difference will be much less for COPD patients departing from that region than for those departing from a region at sea level.

Physiological response to hyperbaric hypoxia

The steps required for oxygen transportation from ambient air to cellular metabolism are numerous, and include: (*i*) alveolar ventilation; (*ii*) matching perfusion of blood with alveolar ventilation; (*iii*) diffusion of oxygen through the alveolar capillary membrane; (*iv*) circulatory ability, i.e. cardiac output of the right ventricle; and (*v*) compensatory oxygen binding to haemoglobin. Changes take place at each of these levels, but should there be an inability to compensate, the patient may be adversely affected by hyperbaric hypoxia.

Hyperventilation is the first compensatory mechanism used by the body for hypoxia.[3] At sea level the tracheal PO_2 is about 149 mmHg, but at 2 450 m it is about 108 mmHg, which represents a decrease of about 27.5%. At this level patients with more severe COPD will already be hyperventilating and may not be able to increase their respiratory rate further. With hyperventilation the alveolar carbon dioxide will diminish. This will decrease the ventilation drive – another factor that may decrease the ventilatory response.

The initial increase in ventilation is due first to an increase in tidal volume and then to an increase in respiratory rate. COPD patients have already increased their tidal volumes; their rate therefore starts to increase sooner than normal.

Ventilation-perfusion relationships are also affected by ascent to altitude. The hyperventilation is matched by the increase in cardiac output and therefore by pulmonary perfusion. Hypoxia and secondary pulmonary vasoconstrictions redistribute the blood flow to lung regions poorly perfused at sea level. This improves the ventilation-perfusion matching.[3]

Diffusion of oxygen through the alveolar-capillary membrane worsens at high altitude. Oxygen flux is dependent on the pressure gradient between the alveolus and the capillary membrane. This equilibrium is time dependent; therefore, as the PaO_2 decreases with altitude, pulmonary transit time may not be adequate for equilibrium of oxygen to take place. This phenomenon is known as diffusion limitation of oxygen transfer of high altitude.[3] Diffusion limitation is exacerbated by exercise, when the pulmonary capillary transit time is further shortened. It is important that COPD patients should not walk around the aircraft more than is absolutely necessary. Attempts should be made to seat them near the toilets.

Cardiac output increases in a linear fashion with hypoxia in an attempt to sustain oxygen delivery owing to the decrease in arterial oxygen content. The increase is initially due to heart rate and then to stroke volume. Pulmonary vascular resistance increases with an increase in altitude owing to pulmonary vasoconstriction caused by hypoxia. This may be critical in COPD patients who may already have raised pulmonary arterial pressure and compromised right ventricular function.

Generally, the decrease in PO_2 represents a small decrease in PaO_2 and a very small decrease in oxygen-carrying capacity, as it is on the flat part of the oxyhaemoglobin dissociation curve. However, in patients with cardiopulmonary disease and a lower baseline PaO_2, the decrease in PO_2 at 2 500 m may cause a dramatically diminished PaO_2, as they may well be on the steep part of the curve.

Pre-flight medical assessment

The value of pre-flight medical assessment has frequently been shown.The Aerospace Medical Association and the British Thoracic Society (BTS) have published comprehensive guidelines for the evaluation and management of patients undertaking flights.[4,5]

A variety of tests have been used to identify patients at risk. These range from easily performed tests, such as arterial blood gas levels and a 6-minute walk test, to a highly sophisticated hypoxia altitude simulation test (HAST), where patients breathe a hypoxic gas mixture of 15.1% oxygen at sea level which simulates breathing air with a PO_2 of 108 mmHg (maximum allowable aircraft cabin pressure). As this test is difficult to perform, the simpler tests have been employed with acceptable results.

The single most important predictor of in-flight PaO_2 is the baseline PaO_2 at ground level. A pre-flight PaO_2 of 70 mmHg is considered to be adequate to achieve a PaO_2 of 50 mmHg at an altitude of 2 540 m. It is recommended that an individual with a PaO_2 of less than 50 mmHg receive supplemental oxygen during a flight. The BTS also recommends that any person with an SpO_2 of less than 92% at sea level be given supplemental oxygen. If the SpO_2 is between 92% and 95% and there are no other risk factors (see below), then the PaO_2 must be above 70 mmHg. If not above 70 mmHg, ideally a HAST should be performed. If not feasible, a 6-minute walk test has been shown to correlate very well with the HAST. Patients who have an SpO_2 of less than 85% during a standard 6-minute walk test should be provided with supplemental oxygen during a flight.[6]

Patients with an SpO_2 of 92 - 95% and the following risk factors require supplemental oxygen:

- an FEV_1 of less than 50% predicted
- lung cancer
- associated restrictive lung disease
- an exacerbation of lung disease within the last 6 weeks
- cardiac or vascular disease
- ventilatory support.

Estimates of inflight PaO_2 can also be determined by several formulae using a multivariate regression analysis:

PaO_2 (alt) = 0.453 PaO_2 (ground) + 0.386 (FEV_1 % predicted) + 2.44

If the patient has an acceptable FEV_1, but a very low diffusion capacity, the following equation should be used:

PaO_2 (8 000 feet) = 0.74 + [0.39 PaO_2 (sea level)] + [0.33 TLCO (% predicted)].

Supplemental oxygen

Patients normally require 2 - 3 litres/minute flow rate. Those already on supplemental oxygen require their rate to be increased by at least 33%. The aim of supplemental oxygen is to keep the PaO_2 greater than 50 mmHg.

Patients are not allowed to bring their own cylinders on board aircraft. The airlines supply cylinders; obviously these arrangements should be made timeously. There are now also some FAA-approved portable oxygen concentrators available, but these must be cleared by the particular airline as policies differ.

Two final important points: remind patients to bring their own medicines and advise them to move around as little as possible during the flight (therefore they have to be seated near the toilets).

References

1. Select Committee on Science and Technology. *Air Travel and Health*. 5th report. London: Parliament, House of Lords, 2000.
2. *Code of Federal Regulations. Title 14 CFR*. Washington DC: US Government Printing Office, 1986.
3. 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(9): 922-927.
4. Air Transport Medicine Committee. Medical Guidelines for air travel. *Aviat Space Environ Med* 2003; 74: A1-9.
5. British Thoracic Society Standards of Care Committee. Managing passengers with respiratory disease planning air travel. BTS recommendations. *Thorax* 2002; 57: 289-304.
6. Mohr LC. Hypoxia during air travel in adults with pulmonary disease. *Am J Med Sci* 2008; 335(1): 71-79.

Indications for and benefits of long-term oxygen therapy in patients with COPD

M J MPE, *MB ChB, FCP (SA)*
Department of Critical Care Medicine, University of Limpopo and Dr George Mukhari Hospital, Pretoria

Hypoxaemia in COPD

COPD primarily affects the lungs and can eventually impair the transfer of oxygen from the atmosphere to the blood. Our lungs contain approximately 300 million alveoli whose ultra-thin walls form the surface for gas exchange. Within the wall of each of these alveoli is a network of blood vessels, the capillaries, which bring blood to this gas exchange surface. In COPD, there is abnormal dilatation of the alveoli, destruction of the alveolar septa and loss of capillary network. These abnormalities adversely affect the capacity of the lungs to receive oxygen and eliminate carbon dioxide. Blood flow and airflow to the alveoli are mismatched. In some alveoli there is adequate blood flow but little air, while in others there is good supply of air but not enough blood flow. When this occurs, fresh air cannot reach certain areas of good blood flow and oxygen cannot enter the blood in normal quantities. Hypoxaemia ensues. In the later stages of COPD the hypoxaemia tends to become more severe.

Mild degrees of hypoxaemia may result in such symptoms as headache, palpitations, breathlessness, worsening angina, restlessness and tremor. Progressive impairment of cognitive function and problems related to the quantity and quality of sleep have been described.[1,2]

The long-term untoward effects of hypoxaemia are secondary polycythaemia, pulmonary hypertension and right ventricular failure.[1] The presence of secondary pulmonary hypertension in COPD increases the risk of hospitalisation and is associated with a grim prognosis.[3,4]

Benefits of oxygen therapy

Supplemental oxygen offers several therapeutic benefits in patients with COPD. Short-term administration during exercise decreases breathlessness and improves exercise capacity in subjects who develop varying degrees of desaturation with exertion.[5] Administration of oxygen during episodes of acute respiratory failure associated with COPD exacerbations has been shown to help prevent the development of respiratory muscle fatigue by decreasing the minute ventilation and the work of breathing.[6]

Long-term oxygen therapy (LTOT) prolongs life in patients with COPD and severe resting hypoxaemia. This benefit was demonstrated by two carefully conducted clinical trials performed more than two decades ago.[7,8] In these two studies, survival appeared to depend on the daily duration of treatment, with better outcome among subjects who received oxygen for more hours per day. The median survival in those receiving O_2 for 18 hours/day was approximately twice that of patients without O_2.

LTOT has also been associated with improvements in mood, neuro-cognitive function, sleep and quality of life.[1]

Indications for LTOT (at least 15 hours/day)

LTOT is indicated in stable COPD subjects who have an arterial partial pressure of oxygen (PaO_2) consistently ≤55 mmHg (7.3 kPa) or SaO_2 ≤88% when at rest, awake and breathing air; or a stable daytime PaO_2 of 56 - 59 mmHg (7.4 - 7.8 kPa) with evidence of cor pulmonale or polycythaemia (haematocrit >55).

Before initiating LTOT, it would be advisable to ensure that the patient is receiving adequate therapy of other kinds for their COPD (e.g. bronchodilators, corticosteroids and treatment of infections). Gas exchange can improve substantially following smoke cessation; therefore assessment for LTOT should be made at least 1 month after the patient has stopped smoking.[9]

It is recommended that the oxygen be used for as many out of the 24 hours as possible. Flows are set at rates needed to maintain a resting partial pressure of oxygen of 60 mmHg, usually 2 l/min, and an arterial oxygen saturation of >90%.

Patients should be adequately informed on how to operate and obtain optimal benefit from their equipment. Patients also need to be sufficiently motivated to undertake the discipline required for oxygen therapy.

LTOT is contraindicated in those who continue to smoke, owing to the increased fire risk and the probability that the poorer prognosis conferred by smoking will offset treatment benefits.[10]

Patients on long-term oxygen therapy need reassessment at some stage after starting therapy, approximately after a month or two. The assessment is both clinical and by measurement of the partial pressures of oxygen and carbon dioxide. A determination can be made of whether the treatment is being used properly and whether it is worthwhile or should be abandoned.

There are three methods of oxygen delivery: oxygen concentrators, cylinders and liquid oxygen systems. At the relatively low flow rates employed, there is no significant difference in the quality of oxygen delivered by the three systems. For most patients, concentrators are favoured.

Pulmonary oxygen toxicity is unlikely to occur at the low flow rates used for LTOT. Increases in the partial pressure of carbon dioxide have been small and well tolerated.[1] Individuals with COPD and

less severe hypoxaemia do not derive any survival benefit from LTOT.[11, 12]

Many of the COPD patients with borderline resting hypoxaemia are likely to have increased oxygen requirements during exertion or sleep.[13] Assessment of the oxygen needs of these patients during these situations may be prudent. In the USA, some medical insurance companies allow prescription of oxygen for certain degree reductions in PaO_2 that occur during exercise or sleep.[1] Further studies are needed to confirm or refute the long-term benefits of oxygen supplementation in these groups of patients.

References

1. Kim V, Benditt JO, Wise RA, Sharafkhanch A. Oxygen therapy in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2008; 5: 513-518.
2. Weitzenblum E, Chaouat A, Kessler R, Oswald M, April M, Krieger J. Sleep and COPD. *Sleep Med Rev* 2004; 8: 253-255.
3. Kesler R, Aller M, Fourgaut G, Mennecier B, Weitzenblum E. Predictive factors of hospitalization for acute exacerbations in a series of 64 patients with chronic obstructive pulmonary disease. *Am J Resp Crit Care Med* 1999; 159: 158-164.
4. Oswald-Mammoiser M, Weitenblum E, Quoix E, *et al*. Prognostic factors in COPD patients receiving long-term oxygen therapy: importance of pulmonary artery pressure. *Chest* 1995; 107: 1193-1198.
5. Somfay A. Porszasz J, Lee SM, Casaburi R. Dose-response effect of oxygen on hyperinflation and exercise endurance in nonhypoxemic COPD patients. *Eur Respir J* 2001; 18: 77-84.
6. Aubier M, Murciano D, Fournier M, Milic-Emily J, Pariente R, Derenne JP. Central respiratory drive in acute respiratory failure of patients with chronic obstructive pulmonary disease. *Am J Resp Crit Care Med* 1980; 122: 191-199.
7. Nocturnal Oxygen Therapy Trial Group. Continuous nocturnal oxygen therapy in hypoxemia chronic obstructive lung disease: a clinical trial. *Ann Intern Med* 1980; 93: 391-398.
8. Medical Research Council Working Party. Long-term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema: Report of the Medical Research Council Working Party. *Lancet* 1981; 1: 681-686.
9. McDonald CF, Crocket AJ, Young IH. Adult domiciliary oxygen therapy. Position statement of the Thoracic Society of Australia and New Zealand. *MJA* 2005: 182: 621-626.
10. Muehibeberger T, Smith MA, Wong L. Domiciliary oxygen and smoking: an explosive combination. *Burns* 1998; 24: 658-660.
11. Gorecka D, Gorzelak K, Sliwinski P, Tobias M, Zielinski J. Effect of long-term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxemia. *Thorax* 1997; 52: 674-679.
12. Granston JM, Crock AJ, Moss JR, Alpers JH. Domiciliary oxygen for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005; 4: CD001744.
13. Mulloy E, McNicholas W. Ventilation and gas exchange during sleep and exercise in severe COPD. *Chest* 1996; 109: 387-394.

Secondary preventive therapy in smoking-related COPD

M L WONG, ***MB BCh, FCP (SA), FCCP, FRCP (Lond)***
Principal Specialist and Head, Division of Pulmonology, Chris Hani Baragwanath Hospital, Johannesburg

Lung function decline in patients who continue to smoke is inexorable. The rate of decline exceeds that which occurs as a normal consequence of ageing, leading to impairment of normal daily activities and quality of life. Despite our current knowledge of COPD, to date there is no known pharmacological agent which abrogates disease progression.

Smoking cessation

The only proven remedy shown to retard deterioration in airflow obstruction is smoking cessation. Since the addictive component of cigarette smoke is nicotine, strategies to combat the smoking habit are largely directed at substituting nicotine intake by pharmacological means, or blocking central nicotine pathways in an attempt to lessen the side-effects of withdrawal. Nicotine itself does not cause COPD; rather it is the myriad of other toxins in inhaled smoke which results in inflammation and lung damage. Most successful quitters have made several prior attempts at smoking cessation, so patients who have failed in the past should be encouraged to try again.

Counselling

Smoking addiction is a complex disease. Apart from the physiological dependence on nicotine, there is also a significant psychological dependence that must be addressed in order to achieve a successful and sustained outcome to smoking cessation. It has been well demonstrated that counselling by doctors or nurses plays an important role and is an essential adjunct to pharmacological therapy. Even brief advice (3 minutes or less) is effective. Counselling specifically made relevant to the patient's illness is more likely to be successful, and must be performed in a non-judgemental and supportive manner. Smokers should be encouraged to set a quit date, rather than attempt gradual reduction. Follow-up counselling (particularly early in the programme) to provide positive reinforcement increases the chances of success. This may even be done telephonically.

Nicotine replacement therapy (NRT)

The principle behind NRT is to ameliorate withdrawal symptoms upon smoking cessation. NRT may be administered by transdermal patch (initial dose 15 mg as daily patch), chewing gum (2 - 4 mg pieces chewed over 30 minutes, up to 60 mg per day), tablets (2 - 4 mg sublingually 1 - 2 hourly, up to 80 mg per day) or spray (1 mg sprayed onto buccal mucosa 1 - 2- hourly). High doses of nicotine must be utilised at initiation of therapy. Failure to do so is a common reason for poor results with NRT, particularly because pharmacological administration of nicotine can never approximate the rapid rise in blood nicotine levels when tobacco smoke is inhaled.[1] The dose of NRT should be gradually reduced over 3 - 6 months. Combination therapy is useful, e.g. transdermal patch to provide a constant level of nicotine, together with chewing gum or sublingual tablets to control sudden urges to smoke. NRT is safe, with caution advised in patients who have had a recent myocardial infarction, unstable angina, recent cerebrovascular accident or transient ischaemic attack, or who are breastfeeding or pregnant.

Bupropion

This sustained-release non-tricyclic antidepressant should be started 1 - 2 weeks prior to the quit date at a dose of 150 mg daily for 3 days, followed by 150 mg bd for up to 6 months. It may be combined with NRT. Reported quit rates at 1 year are approximately 23.1%.[2] It is contraindicated in patients with a history or predisposition to seizures, eating disorders, bipolar mood disorder, and in those who are pregnant or breastfeeding. The most common side-effects are insomnia and dry mouth.

Varenicline

Varenicline is a partial agonist of the nicotinic acetylcholine receptor. Its mechanism of action is to partially stimulate the release of dopamine in the reward centre of the brain, while simultaneously blocking binding of nicotine to the receptors. Studies published to date suggest that varenicline is more effective than bupropion or NRT.[3,4] The recommended dosing schedule is 0.5 mg daily, increasing to the target dose of 1 mg bd during the week preceding the quit date. The drug should be taken for 3 - 6 months.

Adverse effects include nausea (30 - 50%), insomnia and abnormal dreams. Although not available in South Africa at the time of writing, it is anticipated that it will be registered for use in the near future.

Prevention of acute exacerbations of COPD

At least half of acute exacerbations of COPD are precipitated by infections, both viral and bacterial. Patients who experience frequent episodes have a worse outcome due to more rapid decline in lung function. Prophylaxis against commonly occurring infections is therefore likely to be of benefit.

Influenza vaccine

Annual administration of influenza vaccine should be advocated in all patients with COPD. A Cochrane review reported that influenza vaccine reduced exacerbations in COPD, with the protective effect seen 3 or more weeks following administration.[5]

Pneumococcal vaccine

Previous studies suggested no significant impact on morbidity or mortality in patients with COPD vaccinated against *Streptococcus pneumoniae*.[6] However, a recent randomised controlled pilot study demonstrated an additive effect in the prevention of acute exacerbations of COPD in those patients given influenza vaccine and 23-valent pneumococcal vaccine 1 month apart, versus those who received influenza vaccine alone.[7]

It is worth noting that the majority of addicted smokers initiate the habit as teenagers. Campaigns for primary prevention of COPD must be focused at this age group if we are to attenuate the projected increase in smoking-related diseases.

References

1. Henningfield JE. Nicotine medications for smoking cessation. *N Engl J Med* 1995; 333(18): 1196-1203.
2. Hurt RD, Sachs DPL, Glover ED, *et al.* A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med* 1997; 337(17): 1195-1202.
3. Gonzales D, Rennard SI, Nides M, *et al.* Varenicline, an α4ß2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation. A randomized controlled trial. *JAMA* 2006; 296(1): 47-55.
4. Aubin H-J, Bobak A, Britton JR, *et al.* Varenicline versus transdermal nicotine patch for smoking cessation: results from a randomised open-label trial. *Thorax* 2008; 63: 717-724.
5. Poole P, Chacko EE, Wood-Baker R, Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006, Issue 1. Art. No.: CD002733. DOI: 10.1002/14651858. CD002733.pub2.
6. Granger RH, Walters JAE, Poole P, *et al.* Injectable vaccines for preventing pneumococcal infection in patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006, Issue 4. Art. No.: CD001390. DOI: 10.1002/14651858. CD001390.pub2.
7. Furumoto A, Ohkusa Y, Chen M, *et al.* Additive effect of pneumococcal vaccine and influenza vaccine on acute exacerbation in patients with chronic lung disease. *Vaccine* 2008; 26: 4284-4289.

Single Suture

Beat cancer with a healthy lifestyle

Something to tell your patients – a healthy lifestyle may be even more important than you think. The most comprehensive published report on cancer yet has found that eating correctly and taking exercise could prevent more than one-third of common cancers in developed countries and more than a quarter in developing countries.

The report was produced by a panel of the World Cancer Research Fund. These figures do not take into account smoking, which on its own accounts for about a third of all cancers.

The panel examined the largest and most reliable studies to date on how cancer risk is affected by 10 patterns of diet and physical activity, such as eating processed meats or more than 6 g of salt a day, being obese or not exercising regularly. They combined these with estimates of the proportion of people in the UK, USA, China and Brazil who indulge in these risky behaviours.

They found that, at 39%, the UK has the highest proportion of all preventable cancers, followed by the USA at 34%, Brazil at 30% and China at 27%.

New Scientist 7 March 2009: 7.