The effects and potential hazards of exposure to hypoxia in specialised hypoxic rooms or facilities.

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Executive Summary

A hypoxic environment is an environment with a reduced level of oxygen available to breathe whilst maintained at a safe level for human occupation. This report considers the impact of hypoxic environments on persons with specific medical conditions, including heart and lung conditions, asthma, diabetes and pregnancy.

Normal air contains 21% oxygen. This report considers the health effects of entering and working in a hypoxic environment with 15% oxygen. Environments with lower oxygen levels, down to 13% oxygen, have been created for specific purposes. The risk analyses for these are different and are not considered here. Because of normal atmospheric physics, at altitude, air pressure is lower and the partial pressure or availability of oxygen to breathe is lower. At sea level, an environment with 15% oxygen has similar oxygen availability as that at 2400m altitude.

Similar conditions are commonly experienced during commercial aircraft flight. A short-haul flight from Sydney to Melbourne reaches a cabin pressure altitude of 2000 – 2400m but for only a short time during the flight. Longer flights will stay at this cabin altitude for a longer duration. It is highly likely that a hypoxic environment at sea level will be well tolerated by any person who has recently flown without an adverse experience and is not working heavily in the low oxygen environment.

All persons who enter a reduced oxygen environment will have a reduced maximum exercise capacity. Whether this is at all noticeable depends on the background level of fitness and the intensity of work required. Only those patients with severe lung or heart disease are likely to experience undue symptoms in a 15% oxygen room, although all workers should be aware of the risks. A hypoxic room clearly differs from a commercial aircraft, or other high altitude environments, in that a person is able to immediately access normal air by exiting the hypoxic room. This ability to exit the hypoxic environment will resolve the symptoms caused by the environment – thus addressing the rare safety issues that may arise.

In conjunction with policies that control persons being or working alone in a low-oxygen environment, the risks are extremely small.

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Structure of this report

It is intuitive that the low-oxygen room must be dangerous and that there is an inherent hazard in any situation where the level of arterial oxygen is reduced. However, this is untrue for the great majority of those workers and other visitors who may enter or work in the rooms. As this relative safety is somewhat counter-intuitive, much of this review focuses on the physiology that allows humans to accommodate well to this environment and this provides the background to our recommendations.

The Hypoxic Room Environment

A room with 15% oxygen is moderately deficient in oxygen. Air contains 21% oxygen so that at sea level, fully saturated air, has an oxygen partial pressure of 149mmHg. Hypoxic rooms at 15% oxygen have a partial pressure of approximately 110mmHg. During ascent to altitude, barometric pressure declines and by Dalton's law the partial pressure of oxygen must fall. Rooms with 15% oxygen are similar in their oxygen availability to air at an altitude of 2400m[1].

By way of comparison, a range of altitudes and an estimation of how low the inspired oxygen in a room would have to be at sea level to replicate oxygen availability at that altitude are shown in the following table.

Table 1: Examples of high altitude destinations with equivalent pressure of inspired oxygen (P_IO_2) experienced at the barometric pressure.

Location	*Elevation*	P_B	PIO_2	*Equivalent FIO_2 at sea level*
Sea Level	*0*	*760*	*149*	*21%*
Mt Hutt Ski field, NZ	*2086m*	*598*	*115*	*16%*
Aircraft cabin(min)	*2438m*	*574*	*110*	*15%*
Telluride, Colorado	*2600m*	*563*	*108*	*15%*
Cusco, Peru	*3300m*	*518*	*99*	*14%*
Lhasa, Tibet	*3600m*	*499*	*95*	*13%*
Pike's Peak Colorado	*4300m*	*458*	*86*	*12%*
"Lhasa train" peak	*5074m*	*416*	*79*	*11%*
Mt Everest summit	*8848m*	*253*	*43*	*6%*

37°C body temperature, P_B; barometric pressure, PIO_2; partial pressure of inspired oxygen, FIO_2; fraction of inspired oxygen.

In considering the risks of low oxygen rooms, we are therefore fortunate in having considerable experience of these conditions in persons travelling to such altitudes (or higher) and travelling or working in commercial aircraft. It can be seen that a room with 15% oxygen is similar in terms of oxygen availability to many mountain destinations including ski fields where there is a high level of physical activity undertaken by skiers or walkers with a range of physical fitness standards. It is estimated that there are 30 million visitors annually to the American Rocky Mountains alone.

The major way that the hypoxic room differs from either a commercial aircraft or terrestrial moderate altitude is that immediate access is available to 21% oxygen by exiting the room. This will, in a rare circumstance, address a safety issue but it also allows for periods in normal room air to be interspersed with periods of hypoxia in the room or facility.

A summary of the normal physiology of oxygen and energy utilisation

Oxygen is essential for life as it is required to generate energy for all physiological function. Core elements include brain functions, heart(myocardium) activity required to achieve circulation of blood, respiratory muscle work for breathing, and the energy required to keep other tissues including gut, liver and skin alive and functioning. Oxygen demand rises further during any physical activity or locomotor work and also must increase whenever there is a greater demand for ventilation or cardiac output.

In the mammalian circulation, blood enters the lung from the systemic circulation (brain, heart, gut, liver, muscles). This blood is low in oxygen and high in carbon dioxide. The gas within the lung has a higher level of oxygen and oxygen will flow into the blood from the lung if the alveolar oxygen level is higher than that in the pulmonary capillaries (and carbon dioxide will flow in the other direction). Except when there is severe lung disease, oxygen transfer to blood is complete well before the blood leaves the capillary circulation of the lung.

The normal circulation then carries newly oxygenated blood into the systemic circulation. There a gradient exists between blood and the energy dependent tissues and oxygen diffuses down this gradient to be used for metabolism. Oxygen in arteries and capillaries is never fully absorbed by tissues leaving an amount of oxygen left over in the mixed venous circulation.

In health and under resting conditions, there is considerable excess capacity in this system. This is true for ventilation, gas transfer, cardiac output and the extent of peripheral extraction of oxygen[2]. Even in the presence of disease, where the maximum potential for one of these core functions may be reduced compared to normal, the demand on that system at rest will be lower than that maximum sustainable output so that life goes on. What varies most in patients with cardiac and respiratory disease is the extent of reserve capacity.

The core oxygen requirements at sea level breathing normal air can thus be considered as those needed for:

1. Basal work at rest equivalent to that of a normal person
2. Increases in work of breathing or myocardial work related to disease such as
    a. Severe COPD
    b. Valvular heart disease
3. Muscle work associated with locomotor activity
4. The increased work of myocardium and respiratory muscles during incremental exercise required to boost circulation and oxygen delivery

In any person, this leaves many ways that this system can fail or otherwise be unable to further increase its function in the face of demand.

With reduced oxygen availability or inadequate ventilation, alveolar oxygen level falls so that there is a reduced gradient for oxygen to flow into the circulation	COPD Uncontrolled asthma Hypoxic environment
Transfer of oxygen from alveolar gas to the circulation is ineffective or inefficient	Emphysema Pulmonary embolism Severe interstitial lung disease Pulmonary hypertension
The cardiac output required to match the workload cannot be achieved	Systolic or diastolic heart failure Valvular heart disease Ischemic heart disease Angina Uncontrolled hypertension
Oxygen carriage is impaired	Anemia Heavy smoking
Circulation to exercising muscles is impaired	Peripheral vascular disease

Regardless of which of these problems exist the same outcome is seen. Total work capacity is reduced compared to that which would be produced by an optimal system. If oxygen delivery is low, muscles can switch partially to anaerobic metabolism but this is only sustainable to a limited extent.

The Concept Of Symptom-Limited Exercise

This is an important concept of relevance to the hypoxic room environment. Any person who pushes themselves will eventually come to the point that they cannot increase or sustain their workload. Even elite athletes are breathless after a race as we commonly see live or on TV broadcasts.

The symptoms commonly present are breathlessness, fatigue and discomfort in the exercising muscles. These can be present in varying proportions. Thus two patients, one with heart and one with lung disease, may have identical symptoms of breathlessness on exercise. A severely anemic patient would also be breathless on exercise.

These symptoms are important and protective as they prevent us from harming ourselves particularly exercising muscles. They present us with the option of continuing at a slower pace (lower workload) or to stop, rest and then continue.

Normal Physiology At Moderate Altitude

We know for certain that this is a very safe environment from the low rate of adverse events during commercial aircraft flight for travellers, who are mainly at rest, and for cabin attendants who exercise to a moderate degree. The rate of all medical emergencies is 16 per million flights[3]. This is the case even though it is likely that many patients with heart and lung disease do travel with no oxygen and there is not intense cardiopulmonary health screening for cabin attendants who obviously fly frequently and some for long periods. The fundamental protection here for passengers is the low workload.

In a 15% oxygen environment, alveolar and arterial oxygen do fall in healthy people but this is well tolerated[4]. There is a very small increase in ventilation. Normal physiology always defends key functions and operating conditions so that by implication hypoxemia by itself must be well accommodated. Cardiovascular changes are minor. Heart rate at rest increases only by 3bpm at 2400m[5,6]. What this tells us is that maintaining an unchanged oxygen saturation is not critical if there is preservation of an adequate circulation and sufficient oxygen extraction from systemic capillaries.

At higher altitudes or when an exercise task is added, there is a need to increase both ventilation and cardiac output. Hyperventilation becomes essential, for basal and usual exercise tasks, above 3000m at which elevation P_IO_2 is 100mmHg and PaO_2 typically ≈50mmHg[1].

There is a linear decline in maximum work capacity with increasing altitude. At 2400m altitude, or in 15% oxygen, this amounts to 10% in sedentary normal subjects[7]. This applies to everybody. The higher the maximum work capacity at sea level, the higher the workload achievable at higher altitude[8]. The corollary of this is that patients with impaired physiology at sea level, may tolerate altitude or 15% oxygen rooms at rest (such as in an aircraft) but become more symptomatic than a healthy person in performance of a similar work task that both would tolerate well at sea level. In a study of obese patients undergoing moderate-intensity exercise training in 90 minute sessions in a 15% oxygen room, there were no adverse events but the intensity of the work achieved at 60% of their maximum heart rate was lower in hypoxia than that in a comparison group exercising in normal air[9].

It follows also from this that an impaired worker will not be able to complete a heavy workload task in a hypoxic room as easily as under normal conditions. Symptoms will limit this but this is very unlikely to become a safety issue unless the partial completion of the task creates a work safety risk. The more impaired at sea level the lower the workload that will produce symptoms at altitude.

The effect of lung disease in low-oxygen environment

Under hypoxic conditions, a greater degree of arterial hypoxemia is consistently seen in those with pulmonary disease than healthy subjects. During commercial aircraft flight, subjects with pulmonary disease including chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), cystic fibrosis and restrictive disorders experience significant arterial desaturation while seated at rest. With only mildly reduced PaO_2 at sea level ≈78 mmHg, subjects with COPD and ILD experience a PaO_2 ≈48 and 51mmHg mmHg respectively during an AST[10]. In-flight measurements at cabin pressure altitudes near 2400m are similar, with a mean SpO_2 85-86% in subjects with COPD and restrictive lung disease. On Mt Hutt, terrestrial altitude of 2086m, patients with moderate COPD (sea level PaO_2 75mmHg) experienced a resting PaO_2 ≈ 51mmHg[11].

Importantly, altitude and altitude simulation are well tolerated at levels of oxygenation that would and should cause concern in the context of acute medical illness. It is likely that these patients have some reserve in peripheral oxygen extraction so that the actual delivery of oxygen to tissues remains normal or near-normal.

Exercise at altitude leads to further arterial desaturation. PaO_2 with exercise, walking slowly, when breathing 15% oxygen, fell to ≈40mmHg in COPD and to ≈38-40mmHg in patients with restrictive disease. No serious adverse events however were reported. Younger subjects with cystic fibrosis, at a terrestrial altitude of 2650m, desaturate significantly following exercise (PaO_2 <50mmHg) however with no or only minor symptomatology.

While the level of hypoxemia at rest at moderate altitude generally elicits minimal symptoms in subjects with pulmonary disease, physiological impairment becomes evident once a mild exercise task is attempted. During an AST, 70% of subjects with severe COPD and 67% with ILD were unable to complete a 50m walk task. Similarly on Mt Hutt (2086m), some subjects with COPD were unable to complete a 6-min walking task due to dyspnoea, with a mean PaO_2 of 41mmHg, tachycardia to 130bpm and an elevated $PaCO_2$ suggesting true ventilatory limitation. It can therefore be reasonable concluded that patients with severe lung disease will generally tolerate being in a hypoxic room and low activity in that room but will be symptom limited at lower workloads relative to their usual.

Barotrauma

Barotrauma or pressure damage to the lung is a risk during rapid ascent to altitude but is not a risk in hypoxic rooms.

Cardiac disease in a low-oxygen environment

As with pulmonary disease, travel to altitude is generally well tolerated in subjects with cardiac disease. Patients with stable coronary artery disease tolerated travel and exercise atop the Jungfraujoch at 3454m[12]. Similarly at altitudes of up to simulated 3000m, maximal symptom-limited exercise in those with Grade III-IV heart failure did not elicit angina, arrhythmia or ischemia[13]. In the same study, the intensity of exercise was reduced and those with greatest impairment at sea level had the greatest impairment at altitude.

Patients with ischemic left ventricular dysfunction displayed reduced walk distance at 2970m but not at 2000m but without serious adverse events[14]. Repeated exposure for periods of 3-4 hours at altitudes up to 2700m with a training program in patients with moderately severe heart failure was safe and there was a modest improvement in exercise capacity over 10 weeks[15].

There is a lack of evidence in relation to valvular heart disease. The physiology at altitude needs to be considered from basic understanding.

A person with both heart and lung disease and/or other additional co-morbidity

There are a number of potential interactions between heart and lung disease. Similarly to those with pulmonary disease, ineffective ventilation with exercise stress is a feature of chronic cardiac disease. The higher metabolic demand of work of breathing and reduced oxygen transport could cause diaphragm fatigue and compromise limb blood flow, limiting exercise tolerance[16].

What is the effect of a room that is very hot – such as one housing computer servers?

In a hot environment, the amount of total circulation that goes to the skin is increased. Therefore in a hot rather than a cool room, this additional skin flow will deprive exercising muscles of circulation or otherwise require additional myocardial work and work of breathing for a given exercise task. Symptoms would not necessarily be any different but it is that discomfort will be experienced at a lower workload in a hot room. This should be managed with simple fluid replacement and rest breaks from the room. The frequency of these will depend on how hot the room is and the workload required.

What is the effect of a room that is very dry – such as archival storage?

An additional effect is unlikely. In a cold dry environment, there is greater risk for exercise induced asthma in those with poor asthma control and only then at higher workload. This would be addressed rapidly by treatments such as Ventolin or similar.

Specific conditions worthy of further comment

Asthma

Clinically stable asthma is not a contra-indication to travel into or work within a hypoxic environment. Standard asthma guidelines can be used to assess current asthma control. Reliever inhalers such as salbutamol (Ventolin) or terbutaline (Bricanyl) will function normally.

If asthma is poorly controlled, additional breathlessness is likely to be experienced under moderate exercise conditions. Wheeze or breathlessness is possible with higher intensity exercise and would be accentuated if the air is cold and dry[17]. This should be relieved by standard bronchodilator inhalers and exiting the room.

Asthma symptoms in the room would require exclusion and a Specialist report confirming that asthma had been stabilised and that no alternate condition might have contributed to the symptoms experienced(rather than asthma).

Pregnancy

There is very limited evidence in relation to the effect of brief hypoxia. Most of the data is derived from commercial aircraft flight in passengers and cabin attendants. These data are further complicated by some different outcomes known in working vs non-working women. Cabin attendants experience a modest increase in cosmic radiation that is not relevant to this discussion. Aspects of the following guidance are thus poorly evidence based.

After 33 weeks there is reduced fetal growth in babies of mothers resident at altitude. Babies are however born healthy as distinct from other causes of intra-uterine growth retardation. Without evidence to support the argument, a full working week with 40/168 hours in 15% oxygen is unlikely, based on first principles, to cause fetal or maternal harm. In the light of the evidence available we suggest:-

First trimester/uncomplicated pregnancy - no restrictions additional to any imposed by intercurrent disease

Second/third trimester to 34 weeks – visit and light workload as specified elsewhere are reasonable. High intensity workload should be avoided. This may not necessarily be dangerous to mother or baby but there is likely to be more breathlessness given that pregnancy is already a high cardiac output situation.

After 34 weeks

Brief visit/inspection without workload as specified is acceptable. Leave room if respiratory distress develops.

Complicated or high-risk pregnancy

This includes but may not be limited to

- pre-ecclampsia or at increased risk
- pregnancy hypertension
- diabetes
- renal impairment
- severe anemia
- multiple pregnancy
- significant cardiac disease

No outcome data exist. A brief visit to a hypoxic room is very likely safe but should be considered in the category of needless risk. We therefore advise exclusion.

Type 1 Diabetes

Mountaineering to much higher equivalent altitudes has been achieved by people living with well-controlled type 1 diabetes – there being many more practical challenges during trekking[18]. The major concern in the hypoxic room would be unattended hypoglycaemia with the possibility that the experience of hypoglycaemia might be altered or the course more rapid. The principle of not working alone should apply here.

For extended stays (>2 hours), BSL should be checked before entering the environment in low workload conditions and again at 4 hours if work of high intensity is required. There should be the access to a source of sugar should hypoglycaemia symptoms be experienced.

Type 2 Diabetes

The risk of hypoglycaemia is low and the major issue is the need to address relevant cardiovascular risks. There is considerable evidence that exercise in hypoxic environments, in Switzerland and in Austria, for patients at risk of Type 2 diabetes is safe. The altitudes were slightly lower, around 1700m, but the programs included a moderate amount of physical exercise[19]. Exercise in hypoxic conditions actually increases insulin sensitivity and this is a good thing. [20]

Acute Mountain Sickness (High Altitude Illness) In The Context Of Hypoxic Room

A proportion of people will experience acute mountain sickness at 2400m. It may be 10-20% depending on the classification used. AMS will be characterised by headache and one other feature – such as nausea or fatigue as featured in the Lake Louise acute mountain sickness questionnaire. The true altitude effect may be less than this as there is a background frequency of these symptoms at lower altitudes[21]. High altitude illness will only be seen in those who remain in a 15% oxygen room environment for a period of hours at least (but can occur sooner with rapid ascent to higher altitude). In a hypoxic room as described, symptoms may be unpleasant but not life-threatening. We take it that no-one will need to sleep in these rooms. If this were necessary, the effect of altitude on sleep would require consideration.

More concerning in a technical environment would be the potential for subtle high-altitude cerebral symptoms. It is generally agreed that ataxia or subtle cognitive changes are manifestations but usually at altitudes well over 3,000m and no changes in measurable psycholopgical parameters were seen during exposure to 2400m altitudes [22]. This may relevant to workers at risk of greater hypoxemia, such as from pre-existing lung disease, completing complex technical tasks or tasks requiring both a moderate physical workload and high dexterity. Visual deficits can be detected from 1500m and impaired colour perception from 3000m. Thus the 15% oxygen room may produce impairment in low-light vision but it would require the development of a 13% oxygen room for colour vision to be compromised.

There is inter-individual variability in the susceptibility to AMS but a moderately high reproducibility in individuals. Obesity is a risk factor based on studies of workers at altitudes >4000m[23]. Experience of high altitude illness at altitudes much greater than 2400m should not be a disqualifying feature for work in a hypoxic room as the illness is altitude dependent. In the same way, tolerance of a 15% oxygen room may not predict tolerance of 13% oxygen if those rooms are created.

Where a highly technical task is required and the requisite technical skills are limited to an individual who has previously suffered AMS symptoms at 2400m, fragmentation of periods in and out of the hypoxic room should mitigate the risk or discomfort. Where this is impossible, use of a battery powered portable oxygen concentrator would address the individual's symptoms. At a flow rate of 2l/minute given that some of this oxygen will be taken up by the worker, the effect on room oxygen will be trivial. The technical and fire implications would have to be separately considered. We believe this circumstance to be rare indeed.

Relevance of recent travel on commercial aircraft in assessment of risk

In some circumstances, a person being considered for access or work in a 15% oxygen room will have undertaken recent commercial air travel.

Prop-jet aircraft are pressurised but have a cabin pressure higher than that equivalent to a 15 oxygen room. Tolerance of these is not relevant to risk assessment.

Short-haul flights in narrow body aircraft (e.g. Boeing 737 and Airbus 320 series) most commonly have cabin pressure altitudes of 2000-2400m. However on a flight from Sydney to Melbourne that pressure might only be experienced for 10-15 minutes. Pressure is higher during ascent and descent. Considering this, it is highly likely that a brief visit to a 15% oxygen room will be well tolerated by any person who has recently flown without an adverse experience.

Wide body aircraft on long-haul flights will have variable pressure altitudes in the range from 1500-2100m[24]. This is obviously sustained for longer. Most passengers need to walk around the cabin to go the bathroom at least. Considering this, it is highly likely that a visit to a 15% oxygen room and a low level of physical activity will be well tolerated by a person who has recently flown long-haul without an adverse experience and has not experienced a deterioration in cardiac or pulmonary function in flight.

The reverse is also true - that a person who has become distressed in flight should be evaluated by a knowledgeable medical practitioner. Early in the development of long distant plane travel, 8/11 patients admitted to a medical facility near Heathrow airport with heart failure after plane flight had experienced a previous similar event[25].

Management and planning for incidental medical events

This does not feature prominently in other hypoxic room guidance but is relevant.

No matter how careful the screening is, there will be incidental or unpredictable medical events that might occur at any time in life. A severe cardiac or neurological event occurring in a hypoxic environment is likely to be further complicated by hypoxia. A conscious mobile patient would be able to return rapidly to normal conditions by exiting the room but not a person who has collapsed.

This risk can and should be mitigated by "not-working alone" practices. A warning buzzer may not be adequate in all circumstances. This is a Workplace, Health and Safety issue that will have to be managed consistent with the relevant legislation.

Comments on systems and engineering

The hypoxic rooms will be expected to have some degree of inherent leak. In an unoccupied room, as long as oxygen levels are monitored all is well.

In the following combination of circumstances it is possible that oxygen levels will fall and carbon dioxide levels increase over time

- a relatively small hypoxic room
- multiple occupants in the room for some time
- a very good room seal with no or negligible leak

If an occupied room goes below target oxygen concentrations, airflow into the room should be increased not decreased.

Summary of recommendations

A table setting out possible guidance for the key areas of heart and lung disease is attached in Appendix 1.

Summary

Travel to low oxygen environments is generally well tolerated. All workers will have reduced exercise capacity in a 15% oxygen room. In those who have more functional impairment, symptoms will limit exercise capacity at lower workload. If the exercise is terminated, symptoms will resolve as they would after any symptom limited exercise task. Only those patients with severe lung or heart disease are likely to experience undue symptoms in a 15% oxygen room but all workers should be warned.

Therefore, risk assessment and planning must take into account

1. The degree of baseline functional impairment
2. The required intensity of workload

For some people, previous travel to altitude or aircraft flight may provide useful information. However, there is some specialist knowledge required to interpret the latter.

References

1 West JB. The Physiologic Basis of High-Altitude Diseases. Ann Intern Med. 2004;141:789-800.

2 Wolfel EE, Selland MA, Cymerman A et al. O2 extraction maintains O2 uptake during submaximal exercise with ß-adrenergic blockade at 4,300 m. J. Appl. Physiol 1998; 85(3): 1092–1102.

3 Peterson DC, Martin-Gill C, Guyette FX et al. Outcomes of Medical Emergencies on Commercial Airline Flights. N Engl J Med 2013; 368:2075-2083.

4 Kelly PT, Swanney MP, Frampton C, Seccombe LM, Peters MJ, Beckert L. Normobaric hypoxia inhalation test vs response to airline flight in healthy passengers. Aviation Space Environ Medicine 2006; 77: 1143-7.

5 Iwasaki K, Ogawa Y, Aoki K, Saitohi T, Otsubo A, Shibata S. Cardiovascular regulation response to hypoxia during stepwise decreases from 21% to 15% inhaled oxygen. Aviation Space Environ Medicine 2006; 77: 1015-1019.

6 Stowhas A-C, Latshang TD, La Cascio CM et al. Effects of acute exposure to moderate altitude on vascular function, metabolism and systemic inflammation. PLOS One August 2013: e70081.

7 Agostoni P, Cattadori G, Guazzi M, Bussotti M, Conca C, Lomanto M, Marenzi G, Guazzi MD. Effects of simulated altitude-induced hypoxia on exercise capacity in patients with chronic heart failure. Am J Med. 2000 Oct 15;109(6):450-5.

8 Weigle DS, Buben A, Burke CC et al. Adaptation to altitude as a vehicle for experiential learning of physiology by university undergraduates. Adv Physiol Educ 2007; 31: 270-278.

9 Wiesner S, Haufe S, Engeli S, Mutschler H, Haas U, Luft FC1, Jordan J. Influences of Normobaric Hypoxia Training on Physical Fitness and Metabolic Risk Markers in Overweight to Obese Subjects. Obesity 2010:18: 116-120.

10 Seccombe LM, Kelly PT, Wong CK, Rogers PG, Lim S, Peters MJ. Effect of simulated commercial flight on oxygenation in patients with interstitial lung disease and chronic obstructive pulmonary disease. Thorax 2004; 59: 966-970.

11 Kelly PT, Swanney MP, Stanton J, Seccombe LM, Peters MJ, Beckert L. Resting and exercise response to altitude in patients with chronic obstructive pulmonary disease. Aviat Space Environ Med 2009; 80: 102-107.

12 Schmid J-P, Noveanu M, Gaillet R, Hellige G, Wahl A, Saner H. Safety and exercise tolerance of acute high altitude exposure (3454m) among patients with coronary artery disease. Heart 2006; 92:921-925.

13 Agostoni P, Cattadori G, Guazzi M, Bussotti M, Conca C, Lomanto M, Marenzi G, Guazzi MD. Effects of simulated altitude-induced hypoxia on exercise capacity in patients with chronic heart failure. Am J Med. 2000 Oct 15;109(6):450-5.

14 Vona M, Mazzuero G, Lupi A, Vettorato C, Bosso P, Cohen-Solal A. Effects of altitude on effort tolerance in non-acclimatized patients with ischemic left ventricular dysfunction. Eur J Cardiovasc Prev Rehabil. 2006 Aug;13(4):617-24.

15 Saeed O, Bhatia V, Formica P, Browne A, Aldrich TK, Shin JJ, Maybaum S. Improved exercise performance and skeletal muscle strength after simulated altitude exposure: a novel approach for patients with chronic heart failure. J Card Fail. 2012;18:387-91.

16 Calbet JA, Boushel R, Radegran G, Sondergaard H, Wagner PD, Saltin B. Why is VO2 max after altitude acclimatization still reduced despite normalization of arterial O2 content? Am J Physiol Regul Integr Comp Physiol. 2003 Feb;284(2):R304-16.

17 Lee TH, Anderson SD. Heterogeneity of mechanisms in exercise induced asthma. Thorax. 1985 ;40:481-7.

18 de Mol P, de Vries ST, de Koning EJ, Gans RO, Tack CJ, Bilo HJ. Increased insulin requirements during exercise at very high altitude in type 1 diabetes. Diabetes Care. 2011 Mar;34:591-5.

19 Schobersberger W, Schmid P, Lechleitner M et al. , Austrian Moderate Altitude Study 2000 (AMAS 2000). The effects of moderate altitude (1,700 m) on cardiovascular and metabolic variables in patients with metabolic syndrome. Eur J Appl Physiol 2003; 88:506-514.

20 Mackenzie R, et al. Intermittent exercise with and without hypoxia improves insulin sensitivity in individuals with type 2 diabetes" J Clin Endocrinol Metab 2012; DOI: 10.1210/jc.2011-28295.

21 Dallimore J, Foley JA, Valentine P. Background rates of acute mountain sickness-like symptoms at low altitude in adolescents using Lake Louise score. Wilderness Environ Med. 2012 ;23:11-14.

22 Muhm JM, Rock PB, McMullin DL, Jones SP, Lu IL, Eilers KD, Space DR, McMullen A. .S. Effect of Aircraft-Cabin Altitude on Passenger Discomfort. N Engl J Med 2007;357:18-27.

23 Wu TY, Ding SQ, Liu JL et al. Who should not go high: chronic disease and work at altitude during construction of the Qinghai-Tibet railroad. High Alt Med Biol. 2007; 8 :88-107.

24 Kelly PT, Seccombe LM, Rogers PG, Peters MJ. Directly measured cabin pressure conditions during Boeing 747-400 commercial aircraft flights. Respirology 2007; 12: 511-515

25 Beighton PH, Richards PR. Cardiovascular disease in air travellers. Br Heart J 1968; 30: 367-372.

APPENDIX 1

Suggested recommendation

	Brief visit	Low workload	Sustained higher workload
Description	Entering room Being seated Slow inspection walk	Entering room Curator work – sorting, carrying light loads Light manual operating work not normally associated with breathlessness at sea level	Work of moderate intensity that would invoke some breathlessness even if performed at sea level. Examples would include moving furniture, physical installation work, carrying heavy loads
Healthy - no known heart or lung disease	No testing needed	No testing required	No testing required. Fragment work as needed or include periods out of the hypoxic environment titrated to symptoms. If respiratory distress develops a medical review is required before re-entering room to perform similar work.
Mild-moderate chronic lung disease. Estimated VO2max >15ml/min/kg 6MWD >400m	No testing needed if able to walk into room and exit is available. Leave if symptomatic. If clinically unstable visit should be deferred.	Clinical evaluation Lung function tests and resting SaO2 to confirm that severe lung disease is not present because symptoms may not be a reliable guide	Similar evaluation. Must be well at time of work. Task fragmentation if breathless. If respiratory distress develops a medical review is required before re-entering room to perform similar work.

Known severe lung disease. Estimated VO2max <15ml/min/kg 6MWD <50% predicted	No additional testing needed if able to walk into room and exit is available. Leave promptly if symptomatic. If clinically unstable visit must be deferred until medical review confirms return to optimal state.	Not excluded on safety grounds. Medical evaluation required to confirm that the worker is stable at time of first visit. Leave promptly if symptomatic. It is then the worker's responsibility to report any symptom deterioration and seek a medical review before further visits. Previous breathlessness at rest or slow walking preclude further work in the environment. These patients will be more hypoxemic and there is uncertainty about cognitive performance. Highly technical tasks may be compromised.	Excluded in favour of another worker at low risk. In rare event of highly specialised skills being required consider a portable concentrator
Type 1 Diabetes	No testing needed if able to walk into room and exit is available. Should have glucose source – jelly beans or similar. Leave if symptomatic. If clinically stable visit should be deferred.	No testing needed if able to walk into room and exit is available. Should have glucose source – jelly beans or similar. Leave if symptomatic. If clinically stable visit should be deferred.	If an adult should be cleared by Specialist as not having significant heart disease complicating the diabetes If respiratory distress develops a medical review is required before re-entering room to perform similar work.

Asthma	No testing needed if able to walk into room and exit is available. Asthma inhaler should be available. Leave if symptomatic. If clinically unstable visit should be deferred.	Clinical evaluation. Lung function tests and resting SaO2 to confirm that asthma is well controlled. Asthma inhaler should be available	Similar evaluation. Must be well at time of work. Task fragmentation if breathless. Asthma inhaler should be available If respiratory distress develops a medical review is required before re-entering room to perform similar work.
Early Pregnancy	No additional restriction	No additional restriction	No restriction additional to any other disease present. Leave room if distressed and in that situation formal medical review is required before further work in the hypoxic room
Pregnancy - Second/third trimester to 34 weeks	No additional restriction	No additional restriction	High intensity workload should be avoided.
Late pregnancy *(After 34 weeks)*	No additional restriction	No restriction additional to any other disease present. Leave room if distressed and do not work in room again	Exclude
Complicated or high-risk pregnancy	No restriction required but it is a needless small risk. Leave room if distressed and do not re-enter	Exclude	Exclude