Respiratory medicine

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Oxygen therapy

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Oxygen delivery (DO_2) is arguably the most critical requirement for the maintenance of normal organ function and can be illustrated by Equation 1:

$$DO_2 = CaO_2 \times \text{cardiac output}$$

where CaO_2 is total oxygen content, made up largely of oxygen bound to haemoglobin and, to a much smaller degree, oxygen dissolved in plasma. DO_2 therefore depends not only on the degree of oxygenation of the blood but also on cardiovascular function and haemoglobin concentration. Despite its importance, it is not the most tightly regulated physiological parameter for metabolism and gas exchange. This is well illustrated by a study of repeated venesection resulting in isovolaemic anaemia (5 g/dl) in healthy humans.[1] While cardiac output rose, it was insufficient to maintain DO_2 but because of the steep slope of the oxyhaemoglobin dissociation curve at the tissue level, the fall in DO_2 was offset by increased oxygen extraction, indicated by a reduction in mixed venous oxygen (SvO_2).

SvO_2 is therefore a much better indicator of oxygen delivery than arterial saturation (SaO_2), and is one of the targets in resuscitation in sepsis. SaO_2 is readily measurable and helpful in resuscitation, although attention should be paid to integrated physiological function.[2]

The normal ranges of arterial oxygen tension (PaO_2) and SaO_2 are 10–13 kPa and 94–98%, respectively. It is apparent that DO_2 cannot be significantly enhanced by increasing PaO_2 above 16 kPa, where haemoglobin is 100% saturated and the amount of oxygen dissolved in the plasma is small. This manoeuvre will maximise CaO_2 but may not always optimise DO_2.

Oxygen 'toxicity'

There are many reasons why maximising SaO_2 may firstly not optimise DO_2 and secondly may impact adversely on other aspects of a patient's physiology. The best-known example of this occurs during acute exacerbations of chronic obstructive pulmonary disease (COPD). Here PaO_2 above 10 kPa is associated with respiratory acidosis and worse outcomes.[3,4] Decreased hypoxic drive, absorption atelectasis and the Haldane effect (decreased CO_2 buffering by oxyhaemoglobin) all contribute to hypercapnia, but the greatest effect is likely to relate to worsened ventilation-perfusion mismatch. Deoxygenated pulmonary arterial blood is diverted away from areas of diseased lung because alveolar hypoxia due to poor ventilation causes vasoconstriction and thus decreased local perfusion (ie hypoxic pulmonary vasoconstriction). If high-flow oxygen is applied, these alveoli re-oxygenate and reperfuse, but remain poorly ventilated and fail to clear CO_2. In reasonably healthy lungs, regional failure to clear CO_2 can be compensated by an overall increase in ventilation, but impaired respiratory mechanics prohibit this in COPD.

Other adverse effects of hyperoxia relate to effects on the cardiovascular system and the production of reactive oxygen species (discussed in detail elsewhere[5]). Table 1 summarises some of the concepts, with selected references. Hyperbaric oxygen therapy for stroke and intracoronary hyperoxaemic reperfusion for myocardial infarction (MI) are currently being explored. It is possible that the significant rise in oxygen tension in infarcted tissue may outweigh the physiological changes and oxidative stress, but these data are awaited. Studies of supraphysiological DO_2 in critical illness have so far failed to show benefit.[10]

Table 1. The adverse effects of hyperoxia achieved with normobaric oxygen.

Organ/System	Effect of hyperoxia
Pulmonary	• Absorption atelectasis • Release of hypoxic pulmonary vasoconstriction, leading to worsened ventilation/perfusion matching • Decreased ventilation • Pulmonary capillary leak – oxygen toxicity
Cardiovascular	• Coronary vasoconstriction • Increased systemic vascular resistance (increasing cardiac work) • Decreased cardiac output (decreasing O_2 delivery) • Reperfusion injury post-myocardial infarction[6] • Worsened outcomes post-neonatal resuscitation[7]
Neurological	• Neuronal injury post-cardiac arrest in adults[8] • Increased mortality following minor/moderate stroke[9]
Haematological	• Decreased CO_2 buffering by haemoglobin (Haldane effect)

Emergency oxygen use in adults

Guidelines

Recent guidelines for emergency oxygen in adults have been developed under the auspices of the British Thoracic Society (BTS) in association with 21 UK societies.[5] In determining emergency oxygen policy, the committee felt two diametrically opposed philosophical positions could be assumed due to the paucity of evidence:

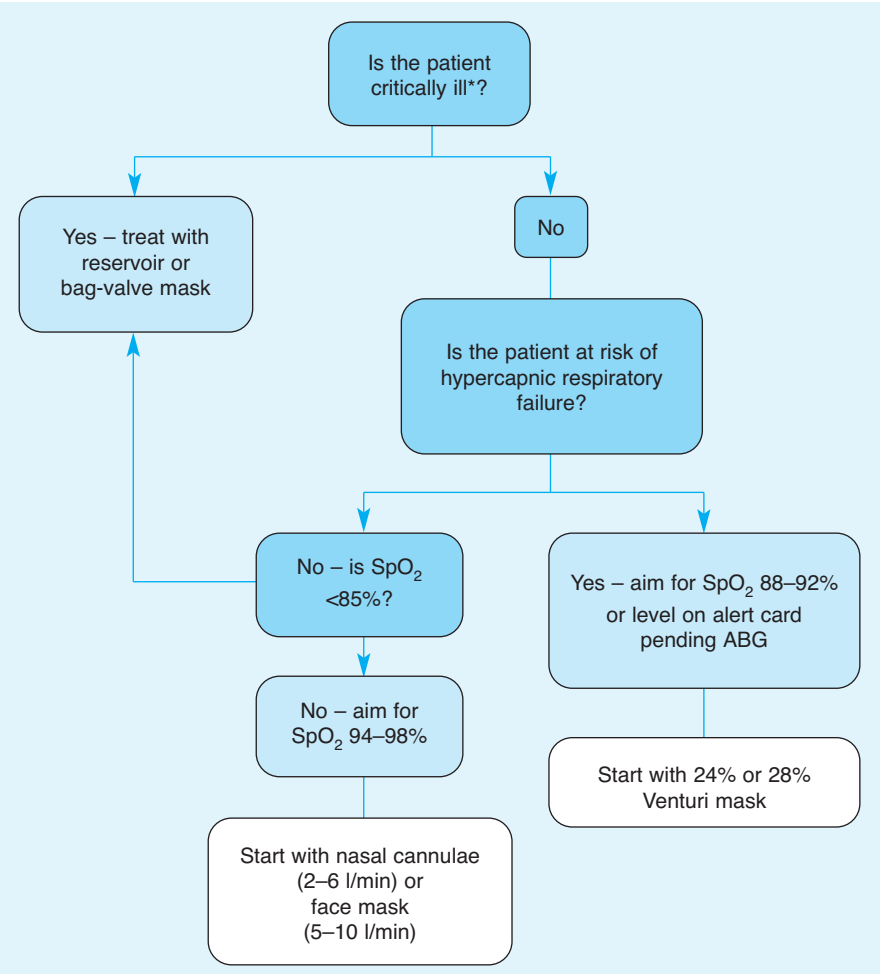
1 *Plentiful oxygen.* Maximising SaO_2 with high-concentration oxygen (HCO) is advisable in many situations, particularly in critical illness when monitoring is unavailable (eg at the roadside). Even when saturations are being monitored, it may be appropriate as other contributors to DO_2 (Equation 1) may not yet be known. Furthermore, it can provide a margin of safety in the event of worsening gas exchange. However, this margin of safety may also mask deterioration[11] since saturations will fall only when the alveolar-arterial gradient is large or the PaO_2/fractional concentration of oxygen in inspired gas (FiO_2) ratio falls below 100. Other clinical features may flag deterioration, but patients who need increasing oxygen to maintain saturations may trigger warning systems earlier.

2 *Oxygen only when needed to achieve normal oxygen saturations*, given the absence of proven benefit of aiming higher and of concerns over the physiological and potentially toxic effects of hyperoxia.

The latter is the position taken by the committee. Notably, in the areas reviewed in Table 1, guidelines from other societies recommend administering oxygen to patients with stroke[12] and MI[13,14] only in the event of hypoxaemia.

Consequently, the guidelines (Fig 1) recognise the necessity for HCO in critical illness, but in other situations recommend that oxygen is given only if saturations fall below the normal range (94–98%).[5] Aligned with the Surviving Sepsis Campaign,[15] the guidelines emphasise that maximised SaO_2 is not synonymous with optimised DO_2 and that vascular filling, haematocrit and cardiac output also need appropriate adjustment.

Exception is made, however, for patients at risk of hypercapnic respiratory



*Critical illness is defined as cardiopulmonary arrest, shock, major trauma and head injury, near-drowning, anaphylaxis, major pulmonary haemorrhage, carbon monoxide poisoning, status epilepticus and other life-threatening emergencies.

Fig 1. Initial algorithm for inhospital prescription of oxygen. ABG = arterial blood gas; SpO_2 = peripheral oxygen saturation.[5]

Key Points

- **Optimisation of oxygen delivery requires more than oxygen therapy and attention should be paid to vascular filling, haematocrit and cardiac output**
- **High-concentration oxygen may cause worse outcomes through physiological effects and reactive oxygen species**
- **Emergency oxygen should be prescribed to a target saturation (88–92% in those at risk of hypercapnic respiratory failure, 94–98% in those not at risk), except in critical illness**
- **Oxygen therapy at home should be assessed, prescribed and followed up by a specialised oxygen service, usually led by a respiratory physician in secondary care**
- **In active patients, ambulatory oxygen should be prescribed to maintain saturations above 90%**

KEY WORDS: chronic obstructive pulmonary disease, hypercapnia, hypoxaemia, oxygen, saturation

failure, typically patients with COPD, but also with neuromuscular and chest wall disorders. The recommended SaO_2 is 88–92%, based on observations that PaO_2 of 7.3–10 kPa is associated with the lowest incidence of acidosis.[3] Patients known to be at risk of hypercapnic respiratory failure should be given an alert card with a prespecified saturation target range, usually 88–92%, although for some this may be lower. Arterial blood gases should guide further management as soon as they are available.

Overzealous withdrawal of HCO may do more harm than good through rebound hypoxaemia. This can be best understood through use of the alveolar gas equation (Equation 2):

$$PAO_2 \approx PIO_2 - PACO_2/RER$$

where RER is the respiratory exchange ratio of O_2 consumption to CO_2 production. When the partial pressure of inspired oxygen (PIO_2) is increased with HCO, alveolar CO_2 ($PACO_2$) will rise. When PIO_2 is reduced to baseline, alveolar PO_2 (PAO_2) will therefore be lower than previously (until the CO_2 body stores are blown off). Consequently, arterial PaO_2 will be lower than prior to HCO. It can be considered conceptually as CO_2 occupying more 'space' in the alveolus. Thus, if an at-risk patient has been given HCO, oxygen should be withdrawn gradually, stepping down through fixed-concentration Venturi masks.

Criticisms of the guidelines

Following these guidelines, there is likely to be further argument about the risk of giving high or low levels of oxygen to patients with COPD. Critics of the lower saturation policy often quote a randomised pilot study of COPD exacerbations in which PaO_2 was titrated to 6.6 kPa in one group and 9 kPa in the other.[16] There was a non-significant trend to worse outcomes in the former group. It is beyond the scope of this article to enumerate all the reasons why this trial cannot be used to justify HCO in COPD exacerbations. One compelling factor, though, is that in neither group was PaO_2 allowed to rise significantly. It was therefore a trial comparing two levels of controlled oxygen. Furthermore, with regard to the effect of the degree of hypercapnic acidosis present in their population on the oxygen dissociation curve (the Bohr effect), target PaO_2 values of 6.6 kPa and 9 kPa theoretically translate to saturations of 74% and 89%, respectively. While, on average, the PaO_2 levels were higher than this, the higher target PaO_2 was actually much closer to the BTS recommendations.

A criticism often levelled at the controlled oxygen protagonist is that the sickest patients require higher concentration oxygen and for this reason there is an association with worse respiratory

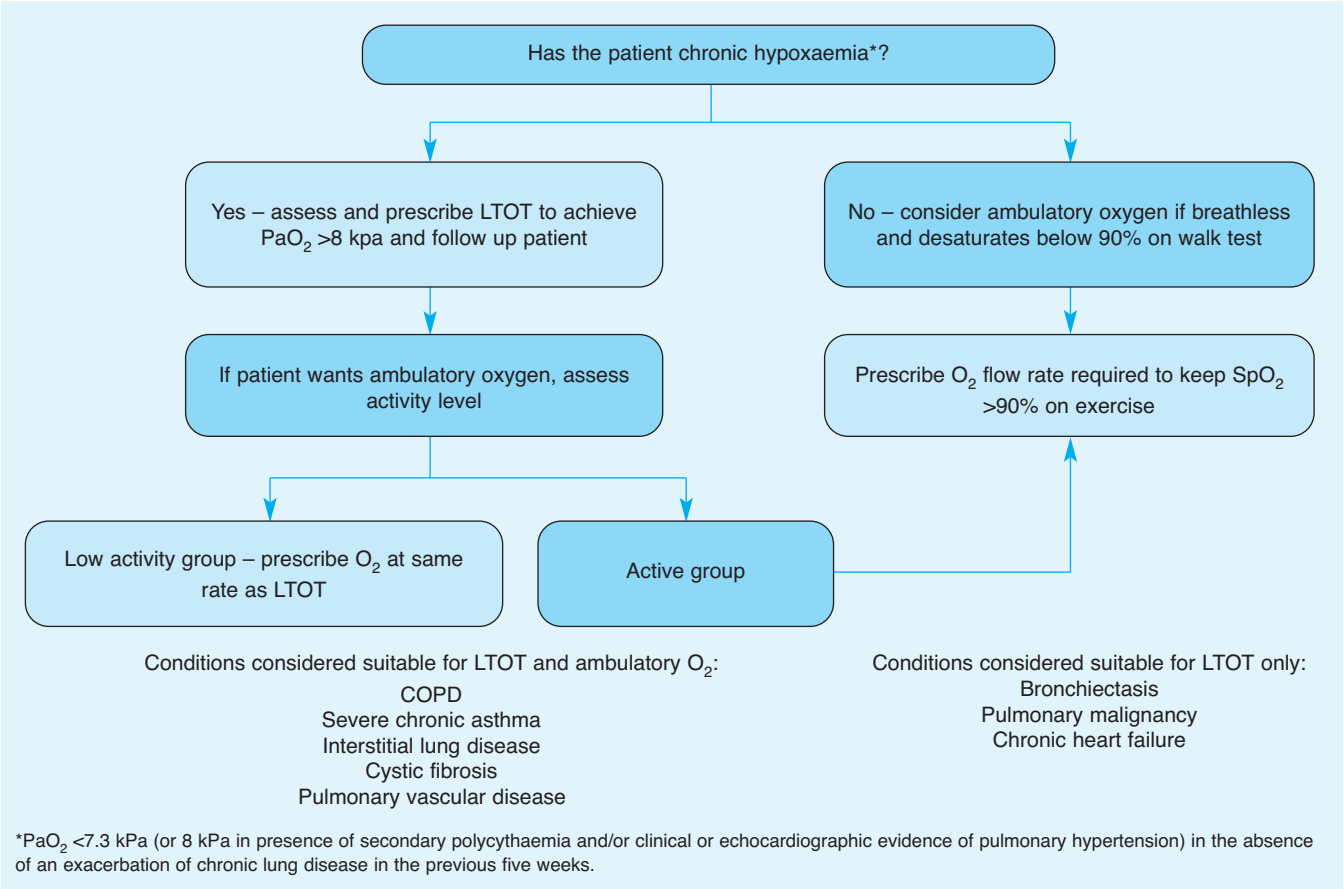


Fig 2. Algorithm for prescription of long-term oxygen therapy (LTOT) and ambulatory oxygen. COPD = chronic obstructive pulmonary disease; PaO_2 = arterial oxygen tension; SpO_2 = peripheral oxygen saturation.

failure. Against this a study from Norwich showed that when a policy of giving 28% oxygen from the outset is instituted, there is no clear increase in complications or significant hypoxaemia.[17] In addition, far fewer patients present with respiratory acidosis.

Oxygen at home

In 2006, a new policy for the prescription of home oxygen, to include long-term, ambulatory and short-burst treatments, was introduced by the Department of Health based on a report by the Royal College of Physicians in 1999.[18] The two key components of the policy were to:

- rationalise oxygen providers, with groups of primary care trusts assigning contracts to one of four companies, and
- move the responsibility of oxygen assessment, prescription and follow up largely to secondary care, with patients assessed by a service directed by a respiratory physician. There is a requirement for a detailed prescription, consent form and record form by the service.

Long-term oxygen therapy

The criteria for long-term oxygen therapy (LTOT) for COPD have been extended to other long-term conditions (Fig 2). If nocturnal hypoventilation is suspected, formal assessment by a respiratory physician is necessary as non-invasive ventilation will be more appropriate in conditions such as neuromuscular and chest wall diseases, rather than oxygen. There is now greater access to ambulatory oxygen, but evidence suggests that, when it is prescribed, many patients use it rarely. A diary card should be provided with the first two-month supply to determine need for continuation.

Patients being assessed for ambulatory oxygen are subdivided into two groups:

- *low activity*: those who are usually immobile and need oxygen for leaving the home. They will need the same oxygen flow rate as their LTOT
- *active*: those likely to benefit from increased exercise capacity. Within this group there will be patients on LTOT and some not, but who desaturate on exercise. Both subgroups should be assessed by six-minute or shuttle-walk testing to titrate the optimal flow rate and to assess the objective improvement in exercise capacity.

Ambulatory therapy is not indicated in chronic heart failure, but desaturation identifies coexistent pulmonary vascular disease and patients may benefit in this instance.

Short-burst therapy provided by cylinders kept in the home and used as required for the relief of breathlessness, may also be prescribed. A recent review, however, suggested little gain to patients with COPD and there is little clear guidance on who will benefit.[19] It remains largely a clinical decision for the relief of breathlessness, but other palliative care approaches should also be considered.

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