

# Should we be giving high concentration oxygen to all patients treated in an ambulance?

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**ABSTRACT** Oxygen is one of the most widely used drugs. It is important to recognise that oxygen administration carries risks as well as benefits. While adequate oxygen saturation of arterial blood is an important factor in tissue oxygen delivery, oxygen administration to patients with chronic obstructive pulmonary disease can lead to decompensated type II respiratory failure. In this debate, Dr Lavery makes the case that high concentration oxygen should be given to all patients treated in an ambulance, while Professor Corris argues against this position.

**KEYWORDS** Oxygen, emergency care, chronic obstructive pulmonary disease, respiratory failure

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## High concentration oxygen should be given to all patients treated in an ambulance

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### INTRODUCTION

The effects of cellular hypoxia include loss of function, cell death and, if widespread within a tissue, infarction and necrosis. Prolonged systemic tissue hypoxia is a frequent precursor to multiple organ dysfunction and death.<sup>1,2</sup> Adequate oxygen saturation of arterial blood is an important factor in tissue oxygen delivery. Despite the above, there are still questions regarding the use of high concentration oxygen (HCO) as a (short-term) first-line treatment for patients travelling by ambulance from the scene of illness or injury.

The origin of this uncertainty is a long-running concern regarding the potential harm caused by oxygen therapy, mainly in patients with chronic obstructive pulmonary disease (COPD).<sup>3,4</sup> A recent randomised controlled trial by Austin et al.<sup>5</sup> recommending the routine titration of oxygen treatment in patients with COPD in the pre-hospital setting has re-ignited the issue.

### THE BENEFITS AND RISKS WITH HIGH CONCENTRATION OXYGEN

It is more than half a century since HCO was found to be potentially harmful in some patients with COPD.<sup>6</sup> In 1980, Aubier et al.<sup>7</sup> found that COPD patients breathing

100% O<sub>2</sub> showed an initial fall in minute ventilation which recovered to approximately normal values after 15 minutes. The small increase in partial pressure of CO<sub>2</sub> (pCO<sub>2</sub>) observed was primarily attributed to ventilation/perfusion (V/Q) mismatch. Decreased minute ventilation<sup>8</sup> and increased deadspace<sup>9</sup> have also been suggested as factors behind HCO-induced hypercapnia. Nevertheless, it is still common, in both pre-hospital and hospital practice, for COPD patients to receive HCO.<sup>10–13</sup> Conversely, many patients with other life-threatening conditions receive too little oxygen.<sup>13</sup>

Oxygen therapy resulting in an excess of oxygen (hyperoxia) may cause significant adverse cardiovascular effects with increased systemic vascular resistance and blood pressure, decreased cardiac output and tissue perfusion.<sup>14</sup> There is also the potential for increased generation of reactive oxygen species which can damage cells. Early studies suggested periods of hyperoxia lasting days rather than minutes might be detrimental.<sup>14–16</sup> Under normobaric conditions, it requires a patient to breath 95% oxygen for 4–22 hours to produce the earliest manifestation of pulmonary toxicity.<sup>17</sup> More recently, relative hyperoxia has been suggested as having beneficial effects in ischaemic myocardium, oedematous brain and in processes such as the inflammatory response in healing and tissue repair.<sup>17</sup>

## THE KEY ISSUES

Should we limit the use of HCO in the pre-hospital setting in order to protect some patients from potential harm while preventing a large number of patients from receiving benefit? We believe that the dilemma can be solved by appropriate application and monitoring of the treatment.

Austin et al. found a 78% reduction in mortality associated with the avoidance of HCO in COPD patients.<sup>5</sup> However, there were oxygen therapy protocol violations in 37% of the 214 patients included in the analysis and only 11% of patients had a blood gas drawn within 30 minutes of arrival in the emergency department as specified by the protocol. In addition, all deaths recorded were attributable to respiratory failure and 70% occurred within five days of hospital admission. This suggests the influence of other factors such as a less aggressive use of invasive or non-invasive ventilation. The latter had previously been shown to decrease mortality associated with acute exacerbations of COPD.<sup>12</sup> However, the decision regarding the pre-hospital use of HCO should not be based on the perceived limitations of a single study.

## OXYGEN AS A DRUG

Oxygen is a drug and we should consider the indications, contraindications and any special precautions needed when administering HCO.<sup>17</sup> We are proposing a strategy which would potentially be applied to all patients in ambulances and so must ensure our deliberations encompass the relative risk of using or withholding HCO, the principle of 'most good for most individuals', the limitations of guidelines and protocols in current clinical practice, and the concept of building reliability in clinical processes.

Tissue hypoxia may be prevented or reversed by increasing poor arterial saturation using HCO, manipulating cardiac preload, contractility or afterload or improving oxygen-carrying capacity. However, monitored fluid loading, infusion of inotropes and use of other vasoactive drugs are interventions not easily achieved as part of pre-hospital care. Increasing oxygen carrying capacity by transfusing blood is relatively ineffective for hours or days due to the low levels of 2,3-diphosphoglycerate in stored red cells (this substance controls the movement of oxygen from red blood cells to body tissues). Thus, augmenting the immediate supply of oxygen is the only rapid, simple and effective method of increasing tissue oxygenation in a pre-hospital setting.

## THE TARGET POPULATION – PATIENTS IN AN AMBULANCE

British Thoracic Society (BTS) guidelines state that patients suffering from major trauma, sepsis, shock, asthma, pneumonia, acute heart failure, pulmonary embolism and

pulmonary fibrosis need 'high flow oxygen' either as an initial treatment, or to correct hypoxaemia (insufficient oxygen in the blood).<sup>18</sup> The guidelines suggest patients with an acute exacerbation of COPD require a more cautious approach using lower concentrations of oxygen. However, the guidelines also recognise that these patients are less responsive to supplemental oxygen when compared with non-COPD patients and so may need a higher dose of oxygen than expected.<sup>2</sup> We should also remember that patients may have other pulmonary conditions co-existing with COPD. The American College of Surgeons recommends HCO for major trauma victims.<sup>19</sup> Other authorities have simply advocated giving sufficient supplemental oxygen to achieve the desired degree of oxygenation.<sup>2,20</sup>

There are other (non-COPD) patients who do not require the use of high concentration oxygen or, possibly, any oxygen at all to treat their condition. The key question is whether such patients would be damaged by the short-term use of HCO in the ambulance. There is no convincing evidence to suggest short-term inhalation of HCO is detrimental to these patients.

Patients with COPD are not a homogeneous group. Some receiving HCO will develop hypercapnia but a large proportion will not.<sup>2,6,8,9</sup> For most COPD patients, significant hypoxia is a more potent and frequent physiological problem than hypercapnia/acidosis.<sup>2,11,21-23</sup>

We have now established that many patients in our target population (patients in an ambulance) will almost certainly benefit from HCO. Some patients with minor illnesses will derive no benefit but also won't experience any detrimental effects. A small proportion (a subset of COPD patients) may suffer harm due to hypercapnia/acidosis but, in such circumstances, the benefit of non-invasive ventilation on outcome is known.<sup>12</sup> It should also be remembered that hypoxia, the more frequent threat in terms of morbidity and mortality, has a much more rapid onset of effect than hypercapnia.<sup>2</sup>

If we were to implement a policy of not using HCO to treat patients with COPD, diagnostic certainty becomes key. There may be lack of objective evidence to support the diagnosis,<sup>24</sup> for example COPD can also be misdiagnosed as asthma.<sup>25</sup> In the Austin study, 405 patients were recruited by pre-hospital personnel as fulfilling the criteria for a diagnosis of acute exacerbation of COPD, but only 214 met the requirements on hospital review.<sup>5</sup> In another study only 58% of patients with COPD were correctly identified in the ambulance.<sup>13</sup>

## THE SOLUTION

Fortunately, there is a way to deliver the benefits of HCO to the majority of patients while avoiding potential harm in the minority. When prescribing a drug, we normally

administer what is viewed as an appropriate dose and, if serious harm is possible due to toxicity, we either monitor the patient to detect early signs of known potential harm or if a 'toxic' level has been established, we monitor drug levels. For the drug oxygen, dosage adjustment and prevention of potential 'toxicity' is readily available through the use of pulse oximetry and appropriate targets for oxygen saturation ( $\text{SpO}_2$ ). In a prospective controlled trial, paramedics used less oxygen on days when they had access to pulse oximetry<sup>26</sup> and in a cost-benefit analysis of pre-hospital pulse oximetry, 441 of 1,787 patients had their oxygen flow reduced or stopped when guided by  $\text{SpO}_2$ , producing a 26% reduction in the total amount of oxygen used.<sup>27</sup>

As discussed earlier, a lack of oxygen at cellular level (hypoxia) is a much more common physiological insult than hypercapnia and will cause morbidity and mortality more rapidly. The appropriate strategy would therefore be to address hypoxia first by starting oxygen at a high dose using HCO and titrating downwards – rather than starting with a low dose and increasing, thus inadvertently prolonging the period of hypoxia. When fractional inspired oxygen (the amount of oxygen that a person is breathing [ $\text{FiO}_2$ ]) is reduced, some COPD patients who have developed respiratory depression show spontaneous correction of both hypercapnia and increased hydrogen ion concentration (low potential hydrogen [pH] levels).<sup>2,28</sup> It is important that downward titration of HCO is an active process, occurring quickly and guided by pulse oximetry and other clinical considerations.

## OXYGEN THERAPY – MAKING CLINICAL PRACTICE RELIABLE

Commencing oxygen at a high dose and using pulse oximetry to (i) monitor saturation and (ii) guide downward titration of oxygen dose delivered, corrects life-threatening hypoxia, potentially reduces the period of tissue hypoxia and reduces the risk of elevated arterial oxygen levels

(arterial hyperoxia) which may promote hypercapnia in some COPD/asthma patients. This approach also allows an early step in airway management to be the same in all patients – the application of HCO.

Consistent early treatment is particularly important. While overall management of illness is often complex, keeping initial interventions simple and uniform is the ideal. This is a fundamental principle of quality improvement and has driven the development of structured practices to be performed collectively, reliably and consistently (care bundles) which improve the reliability of clinical care.<sup>29,30</sup> Complex guidelines and protocols increase the likelihood of low compliance, poor reliability and potentially poor care, as indicated in the Austin study.<sup>4</sup> Austin et al. found that 56% of the patients in the protocol arm of their clinical trial did not receive the correct treatment.<sup>4</sup> In another study only 62% of oxygen-use by ambulance staff was found to fulfil the relevant guidelines.<sup>13</sup>

## CONCLUSION

Keep it simple. All patients should initially receive HCO in the ambulance. This will help ensure the majority who would benefit, do so. Rapid (downward) titration of the oxygen dose should be performed until either an interim  $\text{SpO}_2$  target of 92–94% is reached or the oxygen has been discontinued. At this point the issue of COPD, hypercapnia and hypoxia-dependent respiratory drive can be addressed, particularly if the patient appears more obtunded. Further reduction of the oxygen concentration (dose) in order to achieve a lower  $\text{SpO}_2$  level can then be considered. The difficulty in identifying such patients will be no more difficult (and may be easier) at this point than before any oxygen was administered.

This approach gives clarity to pre-hospital personnel, avoids hypoxia and excessive hyperoxia and makes pre-hospital oxygen therapy simple, uniform, reproducible and reliable.

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## High concentration oxygen should not be given to all patients treated in an ambulance

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### BACKGROUND PHYSIOLOGY

Oxygen was discovered by both Carl Wilhelm Scheele in Uppsala in 1773 and Joseph Priestley in Wiltshire in 1774, working independently, but Priestley is generally given credit because his work was published first.<sup>1</sup> The term 'oxygen' was first used by Antoine Lavoisier in 1777, whose experiments 'helped to discredit the then-popular phlogiston theory of combustion and corrosion'.<sup>1</sup> Oxygen is of course vital for all mammalian cells to survive. Transfer into the body takes place in the alveoli of the lung, and it is transported via the circulatory system, bound to haemoglobin in red blood cells. Oxygen comprises 20.95% of the Earth's atmospheric gas, and though vital to life, to paraphrase Shakespeare, 'too much of a good thing can produce harm'. The definition of a poison includes a 'substance that causes injury, illness or death' and high levels of inspired concentrations of oxygen fulfil all these criteria.

Breathing elevated concentrations of oxygen can lead to hyperoxaemia, with the development of supraphysiological levels of oxygen in body tissues. The body may be affected in different ways depending on the type of hyperoxaemic exposure. Central nervous system toxicity typically occurs following short exposure to high concentrations of oxygen (HCO) at greater than atmospheric pressure. Pulmonary and ocular toxicity result from longer exposure to elevated oxygen levels at normal pressure. Symptoms include disorientation, breathlessness due to lung injury, and abnormalities of vision such as myopia. Prolonged or very high oxygen concentrations can cause oxidative damage to cell membranes, the collapse of the alveoli in the lungs leading to atelectasis and/or retinal detachment and seizures.<sup>2</sup> Oxygen toxicity is managed by reducing the exposure to elevated oxygen concentrations and, usually, recovery occurs in the long-term.

Protocols exist to avoid hyperoxaemia<sup>2</sup> in areas where oxygen is breathed at higher than normal partial pressures, such as underwater diving using compressed breathing gases, hyperbaric medicine, neonatal care and human spaceflights. These protocols have resulted in a decreased incidence of seizures caused by oxygen toxicity, and pulmonary and ocular damage is now predominantly confined to the management of the care of premature infants.

In an acute medical setting, high flow HCO therapy is commonly given to patients on their way to hospital in the ambulance, due to a belief that there are benefits. There is increasing evidence however that many patients who receive HCO may be harmed by this approach.

### CARDIOVASCULAR AND CEREBROVASCULAR DISEASE

Thomson et al. summarised the theoretical risks of hyperoxaemia in vascular diseases of both the heart and central nervous system in an editorial which made a strong case for more trials.<sup>3</sup> Hyperoxaemia may result in coronary vasoconstriction. One randomised double blind trial of the use of oxygen in cases of uncomplicated myocardial infarction found higher rates of sinus tachycardia and a significantly greater rise in cardiac enzymes in the group receiving oxygen, in keeping with a greater infarct size.<sup>4</sup> There was a threefold increase in mortality in patients on oxygen therapy but it did not reach statistical significance (three deaths in 77 patients treated with air versus nine deaths in 80 patients given oxygen at 6 litres per minute [l/min] through a simple face mask for 24 hours). This trial was published in 1976 and oxygen has since been given routinely to millions of normoxaemic patients with myocardial infarction and chest pain for over 30 years without any evidence to support the practice.

Furthermore, a more recent trial showed increased mortality in normoxaemic patients who had strokes of mild to moderate severity in those randomised to receive treatment with oxygen. This result supports the urgent need for large randomised trials of oxygen therapy for non-hypoxaemic patients with acute cardiac and cerebral ischaemia. Thompson et al.<sup>3</sup> have suggested that oxygen should be 'prescribed, administered and monitored with care' in order 'to achieve optimal tissue oxygenation', not maximal oxygenation. This view was proposed by other authors such as Bryan and Jenkinson<sup>5</sup> in the 1980s, but standard medical practice has not taken note of this advice. Because there are no published data suggesting that most medical conditions benefit from hyperoxaemia, and because of the theoretical risks the best evidence-based management should aim for physiological oxygenation.

Aside from the potentially detrimental physiological effects of hyperoxaemia, the toxic effects mediated by reactive oxygen species (ROS) also have potential risks.

Excess ROS, in the form of hydrogen peroxide and superoxide, are generated in the presence of high tissue partial pressures of oxygen ( $PO_2$ ), causing oxidative stress and free radical damage. At physiological levels, ROS act as signalling molecules, but at higher levels they are cytotoxic, notably when released by primed neutrophils as a host defence mechanism.<sup>6</sup> It is thought that ROS are responsible for the development of bronchopulmonary dysplasia in hyperoxygenated ventilated premature infants and for reperfusion injury (post-myocardial infarction and embolic stroke for example).

### CHRONIC RESPIRATORY DISEASE

Although it is important to consider adverse effects of oxygen therapy in cardiovascular and cerebrovascular disease, nowhere is the poisonous property of oxygen therapy administered in the ambulance better demonstrated than when treating exacerbations of chronic obstructive pulmonary disease (COPD). This is a major public health problem in many countries; the World Health Organization for example estimates that 210 million people have moderate to severe COPD and that three million people died of the condition in 2005.<sup>7-10</sup> The costs to healthcare systems worldwide are high.<sup>11-13</sup> The course of the disease is characterised by acute exacerbations, typified by the worsening of three key symptoms, including cough, sputum production and breathlessness. Such exacerbations are a frequent cause of admission to hospital by ambulance. Standard pre-hospital management 'includes nebulised bronchodilators (usually driven by 6-8 l/min of oxygen), corticosteroids, and oxygen'.<sup>1,10,13,14</sup>

High concentrations of administered oxygen to acutely hypoxic patients can save lives by improving severe hypoxaemia. In treating acute non-hypercapnic respiratory failure however, the administration of high flow oxygen to patients without COPD leads to an increase in minute ventilation and a decrease in end tidal carbon dioxide concentration.<sup>14</sup> In susceptible hypoxic patients with stable COPD, hyperoxia leads to a decrease in minute ventilation and an increase in carbon dioxide.<sup>14,17,18</sup> These changes result from both the depression of ventilation and the worsening inequality in the ventilation/perfusion mismatch due to the use of poorly ventilated regions of the lungs.<sup>19</sup>

In 1949, Donald<sup>20</sup> recognised that a proportion of patients with chronic respiratory disease had a tendency to become hypercapnic on high inspired concentrations of oxygen ( $FiO_2$ ). This was confirmed by McNicol and Campbell's 1965 study of arterial blood gases (ABGs) in respiratory failure.<sup>21,22</sup> More than three decades later, in a large, prospective, prevalence study of COPD admissions, Plant et al.<sup>23</sup> showed a strong positive correlation between the severity of respiratory acidosis and the arterial oxygen tension ( $PaO_2$ ). In most hypercapnic patients, a  $PaO_2$  of  $>10$

kilopascals (kPa) was associated with both acidosis and administration of high concentrations of inspired oxygen. Hypercapnia induced in this way can cause severe life-threatening narcosis.<sup>24,26</sup> If high  $\text{FiO}_2$  concentrations are delivered routinely to all patients in ambulances, it is inevitable that a proportion will develop this potentially serious condition. Recent studies indicate that this is a relatively common occurrence in pre-hospital and accident and emergency settings.<sup>26–28</sup> It is also important however to limit the risk of inadequate resuscitation of hypoxic patients who are not at risk of hypercapnia.

Recent studies have shown that the administration of high flow oxygen during acute exacerbations of COPD are associated with increases in mortality, length of hospital stay, requirement for ventilation, and admission to high dependency units.<sup>10,28,29</sup> The use of titrated oxygen treatment has been associated with less acidosis, a lower requirement for assisted ventilation and reduced mortality.<sup>1,29–33</sup>

The Department of Respiratory Medicine at Southend Hospital and the Essex Ambulance Service devised an 'alert card' system to identify individuals known to be at particular risk of retaining carbon dioxide while receiving high  $\text{FiO}_2$ .<sup>23</sup> The scheme has been audited and its effectiveness demonstrated; the strategy is now incorporated into the British Thoracic Society (BTS) emergency oxygen guidelines. They also contributed to the success of the BTS, Salford Royal NHS Foundation Trust and Southend University Hospital NHS Foundation Trust winning a National Patient Safety Award in 2011 ([www.brit-thoracic.org.uk](http://www.brit-thoracic.org.uk)).

The benefits of monitoring the concentration of oxygen delivered in the ambulance setting, rather than routinely delivering a high  $\text{FiO}_2$  to patients with COPD exacerbations, have recently been demonstrated in an Australian study.<sup>10</sup> This was motivated by the need for quantitative evidence to support recommendations for the use of controlled titrated oxygen treatment for patients with an acute exacerbation of COPD. The study compared standard high flow oxygen treatment with titrated oxygen therapy, in the pre-hospital management of patients with an acute exacerbation of COPD.

A significant difference in mortality of patients thought to have COPD was observed between the two treatment arms (relative risk 0.42 for titrated oxygen, 95% confidence interval 0.20 to 0.89;  $p=0.02$ ). Mortality was 9% (21 deaths) in the high flow oxygen arm compared with 4% (seven deaths) in the titrated oxygen arm. In the subgroup with confirmed COPD, there was also a significant difference in mortality: 9% (11 deaths) in the high flow arm compared with 2% (two deaths) in the titrated oxygen arm (relative risk 0.22, 0.05 to 0.91;  $p=0.04$ ). All deaths occurred after the patient had arrived in hospital, including two in the emergency

department and two in the intensive care unit. Hypercapnic respiratory failure was the primary cause of death in all cases, and approximately 70% of deaths in both treatment arms occurred within the first five days of admission.<sup>10</sup>

Many patients, including a proportion of those with chronic respiratory disease, will not develop serious hypercapnic acidosis due to administration of high concentrations of oxygen but some will. Therefore, recognising the dangers of blunderbuss oxygen therapy, the National Institute of Health and Clinical Excellence has recently recommended the use of controlled titrated oxygen delivery in the management of acute exacerbations of COPD, with supplemental oxygen titrated to maintain oxygen saturations at 90–93%.<sup>34</sup> The BTS have also accepted the poisonous qualities of oxygen and have made similar recommendations, but with a target oxygen saturation level of 88–92%.<sup>35</sup>

The delivery of HCO to all hypoxic patients during transfer to hospital, or indeed, to many non-hypoxic patients suffering a stroke or myocardial infarction, will be poisonous to many, and this practice must be stopped immediately. If we are to prevent premature mortality, implementing procedures for preventing oxygen-induced hypercapnoea (and as a consequence, respiratory acidosis) in patients with exacerbations of COPD requires the vertical integration of care from the ambulance service to the emergency room. Evidence to support this view has been available since 1949. Is it not timely that we now practice evidence-based medicine for all such patients?

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