Emergency oxygen therapy for the COPD patient

R Murphy, P Driscoll, R O'Driscoll

Confusion and controversy continues over how much oxygen to give patients with chronic obstructive pulmonary disease (COPD) presenting with breathlessness. This article reviews the published literature dealing with this topic, identifies gaps in the debate that have not been addressed and makes recommendations for future research needed to resolve this issue. Based on this review guidelines for oxygen therapy, based on the best evidence currently available, are then constructed and presented in a subsequent issue.

Literature review

METHODS

Medline from 1966 to 2000 was searched for articles on oxygen therapy and carbon dioxide retention. In addition, colleagues in chest medicine, emergency medicine and intensive care medicine identified reports presented at recent scientific research meetings. As much of the literature on oxygen therapy in COPD was published before 1966, all references made in the literature obtained were examined. Any reports subsequently felt to be relevant, were then also obtained and analysed until it was felt that a complete search had been made.

REVIEW

It is useful to consider the published literature in the light of a series of clinically relevant questions:

What are the perceived dangers of hypoxia and at what Pa_{O_2} does it become dangerous?

Significant hypoxia for more than four to six minutes will cause sudden cardiorespiratory arrest and irreversible damage to the brain and other vital organs. However, it is not known how much hypoxia is required to cause this.

In 1908, Boycott and Haldane showed that a Pa_{O_2} below 45 mm Hg resulted in mental difficulties and memory loss.[1] Later it was found that consciousness was lost at a Pa_{O_2} of about 30 mm Hg.[2 3] Hutchison *et al*, in 1964, commented on this but also noted that acclimatisation to hypoxia is possible, most notably in patients with COPD.[4] Subsequent studies supported this finding and recorded very low Pa_{O_2} levels when these patients have acute exacerbations (tables 1, 2 and 3).

In addition, in a study in 1965, of 81 patients with acute exacerbations of chronic respiratory disease and respiratory failure, it was found that 61 of them had Pa_{O_2} values between 20 and 40 mm Hg and two had values less than 20 mm Hg.[13] In a more recent study in 2000, 13 of 15 patients with COPD developed a Pa_{O_2} less than 50 mm Hg when they undertook light exercise in simulated aircraft cabin conditions.[14] All of these had a Pa_{O_2} above 70 mm Hg when breathing air at sea level. The mean oxygen saturation was 80% during this exercise but all the subjects were asymptomatic. As cardiac and respiratory emergencies are rare during commercial airline flight it is likely that, annually, many COPD patients are exposed to significant hypoxia for up to 12 hours at a time without suffering ill effects.

Consequently, some authors recommend different "safe" levels of hypoxia.[13 15 16] McNichol *et al*, suggested that a Pa_{O_2} of about 20 mm Hg is the lower limit of hypoxaemia compatible with survival, even in COPD patients.[13] Hutchison *et al*, in 1964, suggested that a Pa_{O_2} of 50 mm Hg would prevent immediate death from hypoxia and that oxygen therapy should provide a Pa_{O_2} of at least this level.[4] Later studies have supported this.[17 18]

Table 1 Pa_{O_2} on air in COPD patients when stable

Author	*Patients (n)*	*Mean Pa_{O_2} (mm Hg)*	*Range (mm Hg)*
Mithoefer *et al*, 1967[5]	7	44	38–52
Rudolf *et al*, 1979[6]	10	49	39.5–58.4
Schiff *et al*, 1967[7]	9	52	29–73
Bone *et al*, 1978[8]	10	75	49–104
Bone *et al*, 1978[8]	10	60	42–90

Table 2 Pa_{O_2} on air in COPD patients with acute exacerbations and respiratory failure

Author	*Patients (n)*	*Mean Pa_{O_2} (mm Hg)*	*Range (mm Hg)*
King *et al*, 1973[9]	40	40.4	24–68
Warrell *et al*, 1970[10]	7	29.8	25–28
Rudolf *et al*, 1977[11]	3	33.6	31–39

Table 3 Pa_{O_2} on air in COPD patients when stable and when having acute exacerbations with respiratory failure

Author	*Patients (n)*	*Stable: range/ mean (SD) (mm Hg)*	*Acute: range/ mean (SD) (mm Hg)*
Hutchison *et al*, 1964[4]	9	59–74	23–56
Bone *et al*, 1978[8]	37	54 (8)	41 (9)
Bone *et al*, 1978[8]	13	55 (12)	32 (5)
Agusti *et al*, 1999[12]	18	61.5 (9.1)	47.7 (8.7)

Department of Emergency Medicine, Manchester Royal Infirmary, Oxford Road, Manchester, M13 9WL, UK
R Murphy

Department of Emergency Medicine, Hope Hospital, Salford, UK
P Driscoll.

Department of Chest Medicine, Hope Hospital
R O'Driscoll

Correspondence to:
Dr Murphy
(rossmurphy@doctors.org.uk)

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Key points
- The most dangerous effects of hypoxia are sudden cardiorespiratory arrest and irreversible damage to the vital organs. These effects can occur within minutes.
- The exact level of Pa_{O_2} that is dangerous is unclear but most patients are adequately oxygenated if the Pa_{O_2} is above 50 mm Hg.
- Patients with COPD often have marked hypoxia even when stable and can tolerate this.
- Patients with COPD develop further decreases in Pa_{O_2} with acute exacerbations of their condition. This can be to extremely low levels in some cases.
- Many authors now recommend administering enough oxygen to keep the Pa_{O_2} above 50 mm Hg in these situations.

How much oxygen is required to relieve hypoxia?

In 1960 Campbell predicted the change in arterial oxygenation that would be produced in four patients with hypercapnic respiratory failure by any given oxygen enrichment of the inspired air.[19] He then went on to measure the actual increase in arterial oxygenation when these patients were given oxygen concentrations in the range 24% to 35%. He found that although the increases were, on the whole, less than predicted the differences were not great.[20] Although no exact figures were given it was concluded that these patients were very sensitive to small changes in the concentration of inspired oxygen and that even a concentration of about 25% was certain to produce considerable relief from hypoxia. Campbell reiterated this in 1967 making reference to the oxygen dissociation curve where small changes of Pa_{O_2} in the range 25 to 40 mm Hg produce large changes in oxygen saturation.[16]

Other authors attempted to quantify this effect. Hutchison *et al* found concentrations ranging between 24.4% and 36.4% failed to consistently produce a Pa_{O_2} over 50 mm Hg in 6 of 10 cases of acute hypercapnic respiratory failure.[4] They also plotted the change in oxygen tension against the inspired oxygen concentration and saw a variation in response from patient to patient.

Mithoefer *et al*, in 1967, studied the response of three different groups of patients to 24%, 28% and 35% oxygen.[5] The first was a group of normal patients. The second and third groups were patients with COPD and hypercapnic respiratory failure who were stable and hospitalised respectively. The average level of alveolar oxygen tension produced by each mask in the second group was only about 40% of that found in the first group. In the hospitalised group the arterial oxygen tension was below 50 mm Hg in 70% of patients using the 24% mask, in 35% of those using the 28% mask and in 24% of those using the 35% mask. King *et al*, in 1973, gave 24% oxygen to another group of patients with acute exacerbations of chronic respiratory failure.[9] They recorded a mean Pa_{O_2} of 40.4 mm Hg in these patients on room air and a mean Pa_{O_2} of 57.3 mm Hg after 30 to 60 minutes of 24% oxygen. However, there was a marked variation in the response to oxygen and 15 of 40 patients did not increase their Pa_{O_2} beyond 50 mm Hg. Similar results have been obtained by others.[7 10]

In 1999 Agusti *et al*, gave oxygen to 18 patients with COPD, within 48 hours of an admission with acute respiratory failure.[12] Oxygen was given via nasal prongs at 2–4 l/min and Venturi masks at 24%–28% in a prospective randomised crossover study. These concentrations raised the oxygen saturation to greater than 90% immediately in all cases. Oxygen was administered for 24 hours via each device and the oxygen saturation monitored continuously. Patients subsequently had an oxygen saturation less than 90% for a mean of 3.7 hours using the Venturi mask and 5.4 hours using nasal prongs. In extreme cases patients were poorly oxygenated for as long as 15 hours. It was found that the oxygen saturation was between 70% and 80% for a mean of 80 minutes, between 60% and 70% for a mean of 38 minutes and between 50% and 60% for a mean of four minutes during these periods of poor oxygenation. Again inter-subject variability was considerable.

Key points
- Patients with an acute exacerbation of COPD respond less well to oxygen therapy than normal patients.
- The response to oxygen is variable.
- A number of these patients will not increase their Pa_{O_2} beyond 50 mm Hg on low concentration oxygen.

What are the perceived dangers of carbon dioxide retention and at what $PaCO_2$ does it become dangerous?

The clinical effects of hypercapnia have been known for some time and include depression of neurological and cardiorespiratory function.[21–25]

In 1955, Westlake *et al* described a number of cases where hypercapnia developed in COPD patients after oxygen therapy.[26] One patient lapsed into a coma and fitted. Oxygen therapy was continued for six days and despite stupor, coma and muscular twitching, all related to carbon dioxide retention, the patient survived with no evidence of permanent mental impairment. A second patient developed a rise in Pa_{CO_2}, headache, semi-coma and mental confusion three hours after starting oxygen therapy. This persisted for 24 hours as oxygen therapy was continued and the Pa_{CO_2} increased further. Again, the patient recovered as a compensatory metabolic alkalosis developed. A third patient had a pH of 7.26 and a Pa_{CO_2} of 72 mm Hg on admission with a rise in Pa_{CO_2} to 105 mm Hg and a fall in pH to 7.13 after four hours of oxygen therapy. This was associated with semi-coma and muscular twitching but oxygen therapy was continued. The next day the pH was 7.26 and the Pa_{CO_2} was 93 mm Hg, corresponding with a clinical improvement.

Later during his admission, he relapsed and died after developing a rise in arterial $Paco_2$ to 121 mm Hg and a decrease in pH to 7.12. A fourth patient developed a $Paco_2$ of 110 mm Hg and a pH of 7.16 after 35 hours of oxygen therapy. He slowly sank into a coma and also died. A fifth case was admitted with a pH of 7.33 and a $Paco_2$ of 66 mm Hg. Coma, hypoventilation and cardiac failure developed three hours after starting oxygen therapy corresponding with a pH of 7.07 and a $Paco_2$ of 102 mm Hg. Oxygen therapy was temporarily discontinued and then resumed. Three hours later he had recovered.

Key points

- The most dangerous effects of carbon dioxide retention are depression of neurological and cardiorespiratory function.
- These effects do not occur as quickly as those of hypoxia.
- These effects may last for a period ranging from hours to days and can resolve completely.
- In some cases, however, progressive respiratory failure, a rising $Paco_2$ and a falling pH are eventually fatal.

As the $Paco_2$ and pH are interrelated, it can be difficult to attribute the above effects specifically to one or the other and establish at what levels of $Paco_2$ or pH these changes occur. A number of studies on patients with an acute exacerbation of COPD have shown survival in all patients with a pH over 7.25 and in some with a pH well below this.[4 25–27] In a study published in 2000 Plant *et el* found that a pH less than 7.3 was associated with an increased risk of ICU admission.[28] This suggests that the pH is a much more important indicator of severity and prognosis than the $Paco_2$. Hutchison *et al*, felt that in any stable patient with chronic respiratory failure, it could be assumed that the pH would be above 7.35 and that the rise in $Paco_2$ because of an acute exacerbation would be reflected in a fall in pH below 7.35.[4] Others felt that this was why the symptoms of carbon dioxide narcosis often appear within the first 24 hours of oxygen therapy and then gradually resolve because of renal compensation. However, they also noted cases where the $Paco_2$ increased so slowly that the pH was relatively undisturbed permitting adaptation to hypercapnia.[26] Nevertheless, they felt there was a limit to the changes in $Paco_2$ and pH that could occur without symptoms developing (table 4).

Between these values, the mental state deteriorates as the pH falls and the $Paco_2$ increases.

Table 4 Association between the $Paco_2$, the pH and clinical effects

Authors	*Mental clarity*	*Semi-coma or coma*
Westlake *et al*, 1955[26]	pH >7.3, Pco_2 <80 mm Hg	pH <7.1, $Paco_2$ >120 mm Hg
Sieker *et al*, 1956[25]	pH >7.25, Pco_2 <90 mm Hg	pH <7.14, $Paco_2$ >130 mm Hg

Key points

- The exact levels of $Paco_2$ and pH that are dangerous is unclear.
- Hypercapnia becomes dangerous somewhere in the range 80 to 120 mm Hg.
- Acidaemia is dangerous at a point below a pH of 7.25 and levels less than 7.3 are associated with an increased risk of ICU admission.

Does oxygen therapy cause carbon dioxide retention in patients with COPD or does carbon dioxide retention result from progressive respiratory failure?

In 1949, Donald described the case of a patient with emphysema who lapsed into a coma after 12 hours of oxygen therapy with a $Paco_2$ of 120 mm Hg.[29] After the withdrawal of oxygen this patient recovered rapidly with an abrupt decrease in his $Paco_2$. In 1954 Prime and Westlake observed a decrease in ventilation in 26 out of 35 emphysematous patients after inhalation of pure oxygen with a rise in $Paco_2$ and a decrease in pH.[30] No patients with a normal initial Pao_2 showed increases in $Paco_2$ and not all hypoxic patients had falls in ventilation.

In Westlake's study 40% to 50% oxygen was given to 14 patients admitted with acute exacerbations of chronic bronchitis and emphysema. Most showed increases in $Paco_2$ and decreases in pH.[26] In some, it was again noted that by stopping or decreasing the oxygen and starting or increasing it again, the $Paco_2$ could be made to fall and rise again respectively. In 1960, Campbell described a patient with an acute exacerbation of COPD who received 34% oxygen.[20] This patient increased his oxygen saturation from 44% to 82.5% and his $Paco_2$ rose by 18 mm Hg to 99 mm Hg and he became semi-comatose. He was then given 28% oxygen and the $Paco_2$ decreased to 86.5 mm Hg. The inspired oxygen concentration was then gradually increased to 32% without any problems.

In 1965, McNichol and Campbell found that patients with acute exacerbations of COPD rarely have a $Paco_2$ of more than 80 mm Hg on room air when first admitted and that it is almost impossible for the $Paco_2$ to be above 100 mm Hg or the pH to be below 7.16 unless they have been given oxygen.[13] They questioned why many patients in other studies were found to have a much more severe respiratory acidosis than the patients in their study and related it to hypercapnia developing during the administration of oxygen prior to blood gas analysis. In similar studies, Lal *et al* did not find a $Paco_2$ greater than 80 mm Hg before oxygen therapy and Bradley *et al* found $Paco_2$ values of more than 90 mm Hg in 20 patients, 19 of whom had been given oxygen.[31 32]

In 1967, Campbell stated that these increases in $Paco_2$ as a result of oxygen therapy could be quite large and that the greater the hypoxaemia, the greater the likelihood of a serious increase in hypercapnia.[16] He stated that, based on his own experience, 10% of patients with acute exacerbations of COPD

Table 5 Changes in arterial blood gas measurements in response to oxygen

Subjects	*Treatment*	*Changes*	*Magnitude*
Four patients	100% O_2 for 10 minutes by mask	Four patients—increased $PaCO_2$ Three patients—decreased pH	Range: 2–14 mm Hg Largest decrease: 0.09
Six patients	O_2 1–2 l/min for 10 minutes by nasal cannula	Six patients—increased $PaCO_2$ Five patients—decreased pH	Range: 2–7 mm Hg Largest decrease: 0.05
Five patients	O_2 1–2 l/min for 150–240 minutes by nasal cannula	Four patients—increased $PaCO_2$ Three patients—decreased pH	Range at 30 minutes: minus 2–6 mm Hg Largest decrease at 30 minutes: 0.03

who are given uncontrolled oxygen improve or do not change, 60% develop increases in $PaCO_2$ of about 20 mm Hg over 12 hours and 30% become rapidly unconscious with increases in $PaCO_2$ of more than 30 mm Hg in one hour.

In 1973, Lopez-Majano *et al* tried to assess this in more detail measuring the change in $PaCO_2$ in 151 patients with stable COPD and varied blood gas profiles in response to 100% oxygen for 20 minutes.[33] The mean $PaCO_2$ increased significantly during the first five minutes in all groups. Subsequently there was little further increase in the patients whose initial $PaCO_2$ was less than 50 mm Hg. However, there was a continued increase in patients whose initial $PaCO_2$ was greater than this. Seven out of 20 patients whose initial $PaCO_2$ was greater than 60 mm Hg developed significant respiratory depression and had their tests terminated. Although the group with an initial $PaCO_2$ of less than 50 mm Hg had proportionately a much lower incidence of carbon dioxide retention, three patients in this group showed an increase in $PaCO_2$ greater than 20 mm Hg. The degree of pre-existing hypoxia was correlated significantly with the amount of ventilatory depression during oxygen administration.

In addition, in 1978, Bone *et al*, also felt that they were able to reasonably predict carbon dioxide narcosis in 50 COPD patients in respiratory failure by analysing their pH and Pao_2 on admission.[8] They then used a diagram based on this to predict the risk of carbon dioxide narcosis in another similar group of patients and found that the Pao_2 and pH on admission were reasonably predictive of this outcome.

Key points
- Oxygen can cause carbon dioxide retention in patients with COPD.
- The degree of carbon dioxide retention that develops in response to oxygen is varied.
- Attempts have been made to predict the magnitude of carbon dioxide retention after oxygen from measurements of initial $PaCO_2$, Pao_2, and pH.

Does low concentration oxygen cause less carbon dioxide retention than high concentration oxygen?
In 1960, Campbell hypothesised that when the inspired oxygen concentration of chronically hypoxic patients is increased, they underventilate because they rely mainly on their hypoxic drive to breathe.[16] They continue to hypoventilate until their arterial Pao_2 returns to the initial level. As the respiratory quotient is approximately one, nearly equal volumes of carbon dioxide and oxygen will be exchanged when this happens so that any change in Pao_2 would be exactly equalled by a change in $PaCO_2$ in the opposite direction. Using this logic, he stated that the more oxygen given to these chronically hypoxic patients, the more their $PaCO_2$ would rise.

Over the following few decades, this hypothesis has been questioned and it is now felt that carbon dioxide retention in COPD patients is attributable to a combination of hypoventilation, ventilation-perfusion mismatch and the Haldane effect.[37]

A number of cases have already been described where carbon dioxide retention brought on by oxygen therapy was decreased by lowering the inspired oxygen concentration. In 1962, Massaro *et al* gave different concentrations of inspired oxygen to three groups of stable COPD patients with hypercapnia (table 5).[34]

In three of the patients in the third group the $PaCO_2$ continued to rise and in two, the pH continued to decrease after the initial measurements at 30 minutes. One stabilised at 120 minutes with a maximum change in $PaCO_2$ of 10 mm Hg and a maximum fall in pH of 0.06. The other stabilised at 120 minutes with a maximum change in $PaCO_2$ of 15 mm Hg and a maximum decrease in pH of 0.07. These data would seem to indicate that the higher the concentration of oxygen, the greater the rise in $PaCO_2$ and decrease in pH. However, they also indicate that even patients given low concentrations of oxygen can have large increases in $PaCO_2$ and large decreases in pH and that these may occur over varied periods of time.

In the largest published study of blood gas data in patients with acute exacerbations of COPD, Plant *et al*, in 2000, found a significant negative correlation between pH and Pao_2 in 972 patients after oxygen therapy.[28] This indicates that the more oxygenated these patients become the greater the magnitude of the subsequent respiratory acidosis. In their study 47% of patients were hypercapnic, 20% of patients were acidotic and 4.6% of patients had a pH less than 7.25. More than 50% of hypercapnic patients were acidotic if the Pao_2 was greater than 75 mm Hg. A number of other studies have been performed but it is difficult to compare them as there are variations in the study designs and methods.

In 1967, Schiff *et al* gave 24% oxygen to nine patients with stable COPD who were hypoxic and hypercapnic.[7] The oxygen was given for two to three hours. The average rise in $PaCO_2$ was 2 mm Hg and no patients had a rise greater than 7 mm Hg. The average pH was unchanged. They then went on to give four

patients 35% oxygen for a 40 to 60 minute period. The average $Paco_2$ rose 2 mm Hg and the pH deceased by 0.02.

In 1981, Degaute *et al*, gave 35 patients with acute exacerbations of COPD 28% oxygen for one hour.[35] The average $Paco_2$ rose from 59 mm Hg to 63 mm Hg during that period. In 1970, Warrel *et al* gave seven patients with acute exacerbations of COPD 24.5% and later 28% oxygen with increases in average $Paco_2$ of 4.3 mm Hg at 150 minutes and 7.7 mm Hg at 120 minutes respectively.[10] However, even with these concentrations of oxygen, two patients had excessive rises in arterial $Paco_2$ of 11.8 and 22.2 mm Hg respectively and required artificial ventilation. In 1968, Smith *et al* gave 27 patients with an acute exacerbation of COPD and respiratory failure 24% to 28% oxygen for four hours.[17] Sixteen patients had increases in $Paco_2$ and, in two of these, dangerous respiratory acidosis developed with the pH decreasing to below 7.25. In 1978, Bone *et al* gave 24% to 28% oxygen to 50 patients with an acute exacerbation of COPD and respiratory failure.[8] Thirteen of these required ventilation. In another study, of 73 similar patients, 16 required ventilation after treatment with low concentration oxygen. In 1968, Eldridge *et al* gave oxygen at flow rates ranging from 2 to 12 litres per minute in random order for at least 20 minutes at each level to 19 patients with acute exacerbations of COPD.[36] In 17 patients there were progressive rises in $Paco_2$ with increasing Pao_2 and the $Paco_2$ decreased when the arterial Pao_2 changed from a higher to a lower value. Again, there was great variability in the increases in $Paco_2$ for a given increase in Pao_2 between patients. In 1954, Prime and Westlake *et al* gave 100% oxygen to 35 patients with stable COPD for 30 to 40 minutes.[30] Thirty three had increases in $Paco_2$ ranging from 1.2 to 25.4 mm Hg. Finally, in 1980, Aubier *et al* gave 100% oxygen for 15 minutes to 22 patients with an acute exacerbation of COPD and respiratory failure.[37] There was an average increase in $Paco_2$ of 23 ±5 mm Hg and there was an average decrease in pH from 7.34 ±0.01 to 7.25 ±0.02.

Key points

- There is evidence to suggest that high concentration oxygen causes more carbon dioxide retention and more acidosis than low concentration oxygen.
- The degree to which this occurs has not been quantified. It does not happen in every patient and there is only indirect evidence linking excessive oxygen therapy to an increased risk of death or requirement for mechanical ventilation.
- There is a suggestion that incremental and gradual increases in inspired oxygen may be possible in some patients without major increases in $Paco_2$.
- There is definite evidence that even patients treated with low concentration oxygen may develop progressive carbon dioxide retention and acidosis and require ventilation and die.

How can carbon dioxide narcosis be treated?

It has already been mentioned that some hypercapnia secondary to oxygen therapy may not be harmful and can resolve without any ill effects even with persistent oxygen therapy.[16 26] In addition many cases have been described where decreasing the concentration of inspired oxygen given to patients with acute exacerbations of COPD caused decreases in carbon dioxide retention.[4 16 29] In Plant's study it was observed that most patients who normalised their pH between the emergency department and the ward had had their inspired oxygen concentration reduced implicating this as a very simple and useful method of treating carbon dioxide narcosis.[28]

Respiratory muscle stimulants such as doxapram seem to have fallen out of favour in recent years possibly because of a perceived high incidence of side effects and doubts about their efficacy.[38] However, a recent Cochrane Review, concluding that doxapram is marginally superior to placebo in preventing blood gas deterioration in COPD patients, suggests a possible role as a stop gap until other drugs take effect or where facilities such as non-invasive ventilation do not exist.[39]

Non-invasive ventilation (NIV) seems to be a more effective treatment for carbon dioxide retention. In another study, published in 2000, Plant *et al* compared NIV, in addition to standard treatment, with standard treatment alone in 236 patients with acute exacerbations of COPD who had carbon dioxide retention and a pH between 7.25 and 7.35.[40] They found a greater improvement in pH and a greater reduction in the mortality rate and need for intubation in the NIV group. Similar results have previously been obtained by others.[41 42]

Invasive ventilation is the final option, is accompanied by significant morbidity and may not be appropriate in many severe longstanding cases. However, studies such as that by Martin *et al*, in 1982, which showed a two year survival of 72% in patients with COPD admitted to hospital with respiratory failure suggest that the prognosis is not universally poor and that it should be considered, at least, in all patients refractory to other treatments.[43]

Key points

- Carbon dioxide retention below 80–100 mm Hg may produce no symptoms in some patients, especially if long standing and not associated with acidaemia and may resolve despite continuing oxygen therapy.
- Carbon dioxide narcosis can often be managed by reducing the concentration of inspired oxygen.
- Doxapram may produce a slight and temporary improvement in blood gas indices in some patients.
- Ventilation, by invasive and non-invasive means, are the only other reasonable alternatives at present.

Gaps in the debate that have not been addressed

In the previous sections, some of the clinically relevant issues have been addressed. Nevertheless, several questions still remain unanswered.

Hypoxia is known to be extremely dangerous and when present for more than two to three minutes may cause sudden cardiorespiratory failure and death or irreversible damage to the vital organs. However, we can only estimate the Pa_{O_2} that we should consider dangerous in patients with an acute exacerbation of COPD. Similarly, we know that carbon dioxide retention and the related acidosis is dangerous and may also be fatal but, again,the exact level of Pa_{CO_2} and pH that should be considered dangerous in these patients is not known.

Patients with chronic hypercapnic respiratory failure have chronic hypoxia and their Pa_{O_2} can decrease even further to very low levels during an acute exacerbation of their illness. In these cases small increases in inspired oxygen should increase the Pa_{O_2} but it has been seen that the response to oxygen is, in reality, unpredictable and varied. Although low concentration oxygen has been shown to oxygenate most patients, for most of the day, it can only be estimated what inspired oxygen concentration will guarantee sustained, adequate and safe oxygenation in all patients especially the most severely hypoxic.

Oxygen therapy can cause increases in Pa_{CO_2} and decreases in pH in these patients. Furthermore, high concentration oxygen has been shown to cause more carbon dioxide retention than low concentration oxygen. However, there is no definite evidence to indicate that this results in more deaths from carbon dioxide narcosis and it is not known if a treatment regimen based on low concentration oxygen results in more deaths from hypoxia. There has been no randomised double blind controlled trial comparing the rate of death or the rate of mechanical ventilation of patients with hypercapnic respiratory failure given low or high concentration oxygen. There are also very little data on therapy with high concentration oxygen in these patients indicating problems that might develop and ways that these problems could be avoided or resolved.

Future research

Given this dearth of direct evidence, attempts at grading what we have into "levels of evidence" would seem to be futile.[44] Instead it is hoped that by highlighting this lack of evidence, common to many other areas of emergency medicine, this review will help to define the future research that is needed to improve our understanding and improve our management of these patients.

For a number of reasons it may never be possible to construct trials that directly compare low concentration oxygen with high concentration oxygen. However, it may be possible to compare outcomes of patients treated in accordance with new guidelines, based on the evidence that we do have, with outcomes measured in previous studies or audits to see if these guidelines have resulted in any change for the better.

Similarly, rather than trying to find one simple answer to the question of low concentration oxygen versus high concentration oxygen future research may be best directed at the questions that we have sought answers to in this review, for example, what level of oxygenation really is acceptable in patients with acute exacerbations of COPD? How much oxygen is needed to achieve this? In this way we may then be able to piece together a more comprehensive and precise management protocol using these as building blocks.

Ultimately, whatever way it is done, research that is well designed, concise and focused is much needed to ensure that future reviews of the guidelines presented by the North West Oxygen Group in a subsequent issue are as appropriate and as evidence-based as possible.

Contributors

Ross Murphy and Peter Driscoll initiated the review. Ross Murphy, Peter Driscoll and Ronan O'Driscoll produced the final version of the paper. Ross Murphy acts as guarantor for the paper.

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