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Hot Topic Review

Rapid elimination of CO through the lungs: coming full circle 100 years on

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At the start of the 20th century, CO poisoning was treated by administering a combination of CO_2 and O_2 (carbogen) to stimulate ventilation. This treatment was reported to be highly effective, even reversing the deep coma of severe CO poisoning before patients arrived at the hospital. The efficacy of carbogen in treating CO poisoning was initially attributed to the absorption of CO_2; however, it was eventually realized that the increase in pulmonary ventilation was the predominant factor accelerating clearance of CO from the blood. The inhaled CO_2 in the carbogen stimulated ventilation but prevented hypocapnia and the resulting reductions in cerebral blood flow. By then, however, carbogen treatment for CO poisoning had been abandoned in favour of hyperbaric O_2. Now, a half-century later, there is accumulating evidence that hyperbaric O_2 is not efficacious, most probably because of delays in initiating treatment. We now also know that increases in pulmonary ventilation with O_2-enriched gas can clear CO from the blood as fast, or very nearly as fast, as hyperbaric O_2. Compared with hyperbaric O_2, the technology for accelerating pulmonary clearance of CO with hyperoxic gas is not only portable and inexpensive, but also may be far more effective because treatment can be initiated sooner. In addition, the technology can be distributed more widely, especially in developing countries where the prevalence of CO poisoning is highest. Finally, early pulmonary CO clearance does not delay or preclude any other treatment, including subsequent treatment with hyperbaric O_2.

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Background

At the turn of the 20th century, CO poisoning was treated by administering high concentrations of O_2 to increase the O_2 carried in the blood and, if necessary, ventilation was stimulated by adding CO_2. It was initially and mistakenly thought that patients asphyxiated to unconsciousness by CO had a total body deficit of CO_2 that was replenished by the inhaled CO_2 (Henderson *et al.* 1921). Furthermore, animal tests had shown that the addition of CO_2 to O_2 markedly increased the dissociation of carboxyhaemoglobin (COHb) and accelerated clearance of CO compared with using O_2 alone (Henderson & Haggard, 1920). Carbon dioxide was administered in concentrations of 5–10% in O_2, known as 'carbogen'. From the very beginning, treatment of CO-poisoned patients with carbogen at the site of rescue led to reports of dramatic reversals of coma and other neurological symptoms (Henderson & Haggard, 1922). In short order, the administration of carbogen became the standard of care for CO poisoning, and remained so for almost a half-century. Indeed, carbogen remains a stock item in many hospitals to this day.

Hyperbaric oxygen

By the 1960s, the rationale for using carbogen for CO poisoning was increasingly questioned (Donald & Paton, 1955). The notion that CO poisoning was accompanied

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by a deficit of CO_2 was rejected (Donald & Paton, 1955). Ventilatory stimulation by CO_2 was no longer required, because hypoventilation accompanying coma could be managed by endotracheal intubation and mechanical ventilation. It became feasible to increase CO dissociation from haemoglobin (Hb) by exploiting the mass action effect of O_2 on the equilibrium (Haldane, 1895) $COHb + O_2 \overset{\leftarrow}{\rightarrow} O_2Hb + CO$ by administering the O_2 at hyperbaric pressures (Pace *et al.* 1950). Hyperbaric O_2 replaced carbogen as the preferred treatment (Smith, 1962) because it was thought (mistakenly, as subsequently demonstrated; Fisher *et al.* 1999) to result in faster CO elimination (Norman & Ledingham, 1967) and, on theoretical grounds, to be effective at reversing the assumed toxic effects of CO in such extravascular tissues as the brain (Brown & Piantadosi, 1990; Stoller, 2007).

Time to treatment over type of treatment

> *The point cannot be too strongly emphasized that for treatment to be effective it must be applied at the earliest possible moment after the victim is discovered, and must remove the carbon monoxide from his blood as soon as possible.* (Henderson & Haggard, 1922)

Although the physics and chemistry underpinning the effectiveness of hyperbaric O_2 in clearing CO from the blood are unassailable, and some beneficial effects can be demonstrated in animals (Brown & Piantadosi, 1990, 1992; Piantadosi *et al.* 1997), in practice it has been difficult to demonstrate its clinical efficacy. The poor response of most victims of CO poisoning to hyperbaric O_2 has been confirmed repeatedly by expert panels in Australia, Canada and the USA (Buckley *et al.* 2005; Juurlink *et al.* 2005; McMaster University Division of Emergency Medicine, 2006; Wolf *et al.* 2008), as well as large controlled trials in Australia (Scheinkestel *et al.* 1999) and France (Annane *et al.* 2010). The primary lesson to be learned from the discrepancies between animal and clinical studies is that for patients poisoned by CO, the time to treatment, rather than the method of treatment, is of major importance (Gorman *et al.* 1992; Scheinkestel *et al.* 1999). Even from the very beginning of hyperbaric O_2 treatment of CO poisoning in Glasgow, it was clear that delays between poisoning and treatment markedly reduced its effectiveness (Smith, 1962). Times to treatment as short as 3–6 h, which are all that can be expected for hyperbaric O_2 given the logistics of patient transport and chamber preparation, continue to show no benefit compared with normobaric O_2 (Scheinkestel *et al.* 1999; Annane *et al.* 2010).

Effect of time to treatment on pathology of CO poisoning

It has been long understood that 'asphyxia is not immediately terminated when the victim is removed from the gassing chamber. . .although his body may be surrounded and his lungs filled with fresh air, his brain continues to be asphyxiated' (Henderson & Haggard, 1922). Eventually, there is a redistribution of CO from blood to extravascular tissues (Coburn, 1970), drawn there by the high affinity of some cellular molecules for CO [e.g. myoglobin in heart muscle (Coburn, 1970; Dolan, 1985) and cytochromes in the brain (Cronje *et al.* 2004)], even at low [COHb], and particularly with hypoxaemia (Dolan, 1985).

One instructive model of CO distribution kinetics to an extravascular compartment is CO in the fetus, as studied by Longo and colleagues (Hill *et al.* 1977; Longo & Hill, 1977) in pregnant sheep. Fetal Hb has a higher affinity for both O_2 and CO than maternal Hb. After an initial maternal exposure to CO, there is a delay in the transfer of CO to the fetus of about 1 h (Longo & Hill, 1977), which is characteristic of many tissues (Cronje *et al.* 2004). This delay is due to the low partial pressure of CO (P_{CO}) in the plasma, because it is tightly bound to Hb (Bruce *et al.* 2008). Eventually, at higher [COHb], P_{CO} rises and CO begins to diffuse into the tissues. At equilibrium, fetal [COHb] will exceed maternal [COHb] (dotted lines in Fig. 1). If rescue occurs prior to equilibration of CO, maternal [COHb] will follow the time course illustrated in Fig. 1. If normobaric O_2 is administered, the maternal half-time of CO elimination will be ~80 min (Dolan, 1985). However, because of the greater affinity of fetal Hb for CO, fetal [COHb] will continue to rise and so exceed

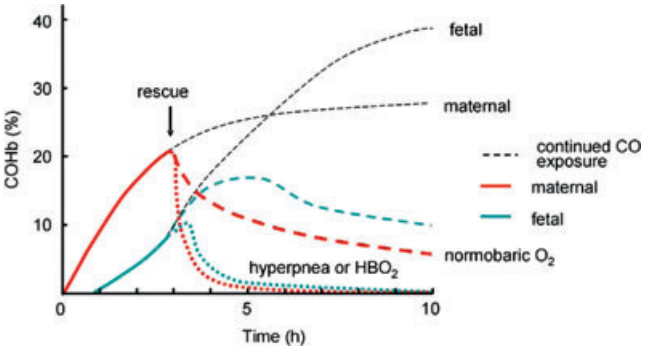

Figure 1. Schematic diagram illustrating the kinetics of [COHb] in mother (red) and fetus (teal) after 3 h exposure to CO and then rescue
Black dotted lines represent [COHb] at equilibrium; coloured dashed lines represent [COHb] with normobaric O_2 treatment; coloured dotted lines represent [COHb] with accelerated CO clearance. (Figure from Rucker & Fisher, 2006, with permission. Labels added to original figure by the authors.)

that of the mother, even as her [COHb] is falling. If CO clearance from the mother is accelerated, the P_{CO} gradient between the fetus and mother increases (Longo & Hill, 1977), thereby also increasing the rate of elimination from the fetus. A computer simulation of CO kinetics between mother and fetus using the model proposed by Hill & Longo (1977) is available as a supplemental file entitled CO Model.zip.

These principles of CO kinetics have long been acknowledged (Henderson & Haggard, 1922; Smith, 1962; Scheinkestel *et al.* 1999); yet somehow, by consensus, a treatment that was highly effective because it could be administered with the least delay (carbogen) was abandoned for another (hyperbaric O_2) despite its associated delay in treatment. The (presumed) greater rate of CO elimination and the potential of reversing CO-related pathology (Sharp *et al.* 1962) with hyperbaric O_2 was considered an acceptable trade-off for the difficult logistics, increased expense and added delay in treatment. Despite little evidence of its value, hyperbaric O_2 has remained the mainstay of treatment for the last half a century.

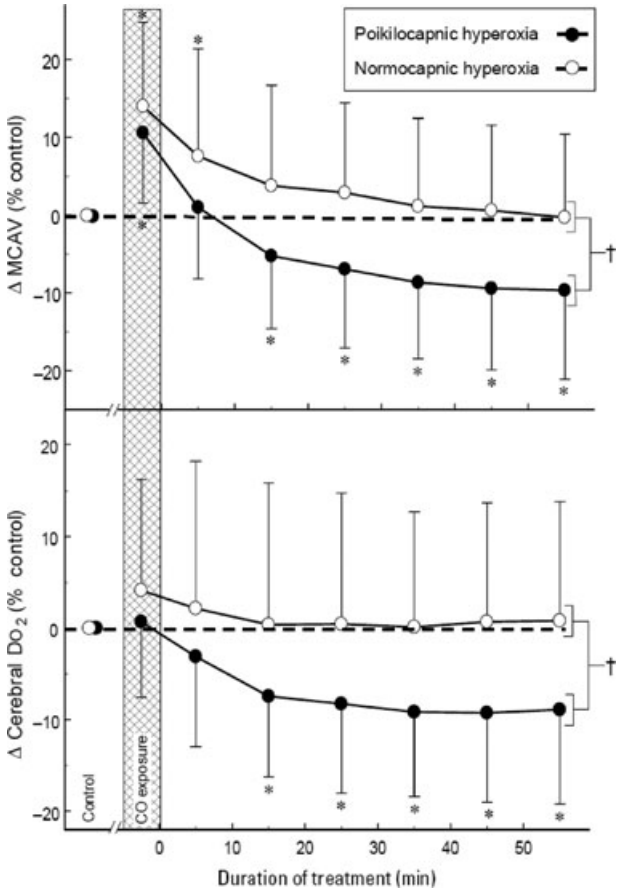

Figure 2. Effect of poikilocapnic and isocapnic normobaric O_2 treatment on cerebral O_2 delivery (DO_2) in CO-exposed human subjects
Fourteen human subjects were exposed on two separate occasions to CO until their [COHb] reached 10–12%. They were administered 100% O_2 with, and without, maintaining isocapnia. Blood O_2 delivery was calculated from arterial PO_2, arterial P_{CO_2}, haemoglobin saturation (11–[COHb]), plasma O_2 content, and changes in middle cerebral artery flow velocity (MCAV) as measured by transcranial Doppler (as a surrogate of change in cerebral blood flow). Poikilocapnic hyperoxia resulted in a significantly lower DO_2. (From Rucker *et al.* 2002, with permission from the publisher.)

Is normobaric oxygen a standard of care?

Even normobaric O_2 treatment of CO poisoning is problematic. The effect of P_{O_2} on the half-time of [COHb] reduction in patients treated in hospital (as opposed to laboratory volunteers) is highly unreliable ($r^2 = 0.19$), ranging from 26 to 148 min (Weaver *et al.* 2000). Furthermore, normobaric O_2 treatment may even contribute to the morbidity of CO poisoning. Apart from the potential for free radical generation by hyperoxia (Thom, 1990), there is also the underappreciated effect of hyperoxia as a ventilatory stimulant. Hyperoxia-induced hyperventilation results in some degree of hypocapnia (Becker *et al.* 1996), which is associated with a reduction of blood flow in such CO_2-responsive vascular beds as the coronary (Case *et al.* 1975) and cerebral circulations. The reduction in cerebral (Kety & Schmidt, 1948) blood flow with hypocapnia occurs even in the presence of increased levels of CO in the blood (Rucker *et al.* 2002). In normoxic individuals, as well as those with high [COHb] (Henderson & Haggard, 1922), normobaric O_2 produces only a very small increase in blood O_2 content that is carried in the plasma, where it is poorly soluble. If this small increase in blood O_2 content is accompanied by even a small reduction in tissue blood flow, the result can be a net reduction in organ O_2 delivery (Case *et al.* 1975; Rucker *et al.* 2002). Figure 2 illustrates that the administration of normobaric O_2, an undisputed treatment for CO poisoning since the time of Haldane (Haldane, 1895), may even exacerbate the brain ischaemia resulting from CO poisoning.

Back to the future

If there are problems with carbogen, hyperbaric and normobaric O_2, where do we go from here?

Increased alveolar ventilation can be as effective as hyperbaric O_2

About a decade ago, the trade-offs between rate of CO elimination and time to treatment were re-examined. The initial studies compared the half-times of reduction of [COHb] induced by increases in alveolar ventilation with those resulting from hyperbaric O_2. Previous studies (Henderson & Haggard, 1920) had concentrated on the

relative efficacies of various mixtures of CO_2 in O_2 for reducing [COHb] in spontaneously breathing animals (Walton *et al.* 1925) and humans (Henderson & Haggard, 1922). In the early 1960s, it became apparent that the elimination of rebreathing during assisted ventilation (Douglas *et al.* 1961) and the magnitude of the minute ventilation (Killick & Marchant, 1959), i.e. the net alveolar ventilation, rather than the concentration of CO_2 in the carbogen, was the main factor determining the half-time of elimination. Indeed, with controlled ventilation Fisher *et al.* (1999) demonstrated, in dogs, that isocapnic increases in alveolar ventilation result in the same half-times of CO elimination as those for hyperbaric O_2 (Fig. 3).

Favourable CO kinetics with increased alveolar ventilation

Takeuchi *et al.* (2000) then investigated CO elimination half-times in spontaneously breathing human volunteers exposed to CO. Subjects breathed O_2 using a circuit that maintained normocapnia. Several findings from this study are of interest. First, the ventilatory response to normobaric O_2 (open symbols in Fig. 4) varied between subjects. Second, the relationship between elimination half-times and minute ventilation is a rectangular hyperbola. This shape means that initial graded increases in minute ventilation above resting values result in the greatest reductions in half-times. For example, a 70 kg patient ventilating at about 15–20 l min^{-1} (levels easily tolerated by patients without severe lung disease) can reduce the half-time to a value similar to that reported for hyperbaric O_2 (Takeuchi *et al.* 2000). Finally, the relationship between minute ventilation and elimination half-time is scalable to body size and sex (Tesler, 2000).

Back to carbogen?

Is it therefore appropriate to resurrect carbogen as a readily deployable means to increase alveolar ventilation without reducing arterial P_{CO_2}? Unfortunately, it is not. As early as 1955, an official report to the Medical Research Council (UK) (Donald & Paton, 1955) warned about the risk of exacerbating acidosis by administering carbogen to patients who are already retaining CO_2 due to ventilatory depression from severe CO poisoning or previously ingested drugs. As for those patients with an intact ventilatory response to CO_2, administration of CO_2 up to a concentration of 4% increases the minute ventilation only by a factor of two (Soley *et al.* 1941), thereby limiting its effectiveness in CO elimination. Moreover, large individual variations in ventilatory responses to inhaled CO_2 (Solely *et al.* 1941; Prisman *et al.* 2007) mean that

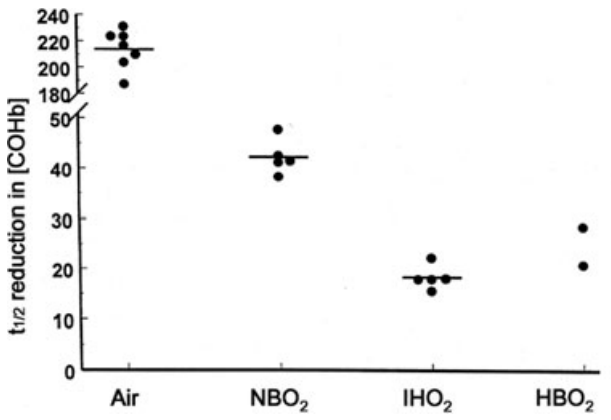

Figure 3. Elimination half-times for [COHb]
Five anaesthetized, intubated, spontaneously breathing dogs were exposed to CO until [COHb] reached ~70%. They were then administered, sequentially, room air (Air), normobaric O_2 (NBO_2) and then vigorously mechanically ventilated with O_2 while maintaining normocapnia (IHO_2). Blood was drawn every 5 min and analysed for [COHb]. Plots of log [COHb] *versus* time were used to calculate the half-times of reduction in [COHb]. Values are compared with dogs prepared in a similar manner and treated with normocapnic ventilation with O_2 at 3 atm (304 kPa). Isocapnic hyperpnoea resulted in a similar rate of [COHb] reduction to hyperbaric O_2 (HBO_2). Reprinted with permission of the American Thoracic Society. Copyright © American Thoracic Society. Hyperbaric data from the original study reported in the text was added to the figure by the authors.

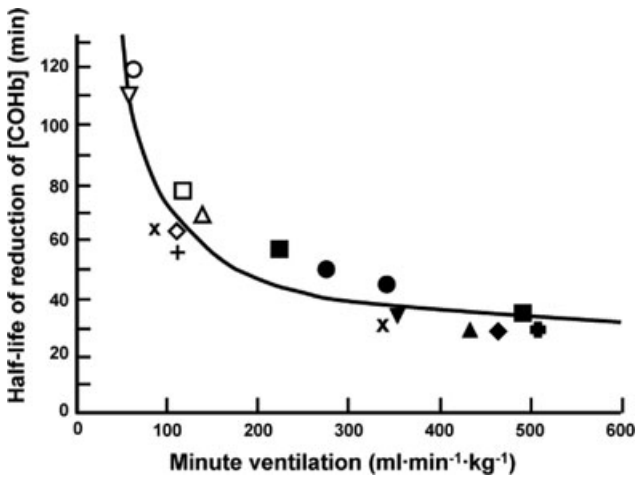

Figure 4. Half-time of COHb reduction *versus* minute ventilation in humans
Seven men were exposed to CO until [COHb] reached 10–12% on two separate occasions. On one occasion, subjects breathed 100% O_2 ('resting ventilation'). On the other occasion, subjects were administered 100% O_2 and asked to increase their minute ventilation; on that occasion, isocapnia was maintained. Venous blood was drawn every 5 min and analysed for [COHb]. Open symbols represent values during resting ventilation (normobaric O_2); filled symbols during normocapnic hyperpnoea. Half-times of elimination were calculated from plots of log [COHb] *versus* time. Most of the increase in [COHb] reduction was reached at a relatively modest 200 ml min^{-1} kg^{-1}, or 14 l min^{-1} for a 70 kg person. (From Takeuchi *et al.* 2000; reprinted with permission of the American Thoracic Society. Copyright © American Thoracic Society.)

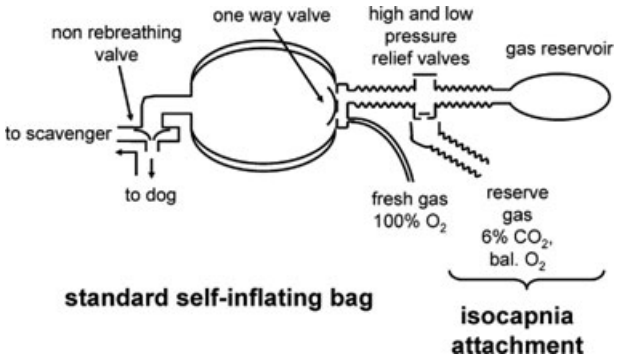

Figure 5. A self-inflating bag circuit suitable for spontaneous and controlled ventilation
Reserve gas enters circuit through the inspiratory relief valve of the self inflating bag (modified from Fig. 1 of Sasano *et al.* 2001; figure reproduced with permission of the publisher.)

one cannot guarantee an increased rate of CO elimination, or even that hypocapnia will be prevented (Baddeley *et al.* 2000; Prisman *et al.* 2007). Above an inspired CO_2 concentration of 4%, minute ventilation markedly increases, but so does respiratory distress (Baddeley *et al.* 2000); these investigators found that 30% of patients and healthy subjects were unable to tolerate 5% CO_2. It is therefore unlikely that a single premixed carbogen dose will fit all.

Hyperpnoea without carbogen

It follows from the preceding discussion that exploiting an increase in alveolar ventilation to clear the blood of CO will require a different approach. The method used must maintain normocapnia in order to allow patients to sustain increased ventilation comfortably for two to three half-times of CO elimination, thereby achieving more complete elimination of CO. Rather than administering a fixed concentration of CO_2 in an attempt to maintain normocapnia with hyperpnoea, one can administer CO_2 in direct proportion to increases in minute ventilation above basal levels (Sommer *et al.* 1998). Ideally, the apparatus that would be used to maintain normocapnia would be safe, easy to use, portable and, if at all possible, inexpensive.

Increasing alveolar ventilation while maintaining normocapnia

Historically, the advances in treatment of CO poisoning were also linked to the fabrication of devices required to implement them. Henderson and Haggard in New York devised their H-H Infusor to administer carbogen (Henderson & Haggard, 1922). Smith and Sharp (1960) built the first fixed and then portable hyperbaric chambers (Norman *et al.* 1970) in the Aberdeen Royal Infirmary, in Scotland. Recently, researchers in our laboratory (Sommer *et al.* 1998) described a method that passively maintains normocapnia regardless of minute ventilation and pattern of breathing. In that circuit, a constant O_2 flow is provided to a standard self-inflating bag, and the inspiratory relief valve of the self-inflating bag is attached to a demand regulator supplying 6% CO_2 in O_2 (Fig. 5). Any increase in minute ventilation above the O_2 flow is therefore supplied by the demand regulator (6% CO_2 in O_2). The O_2 flow is

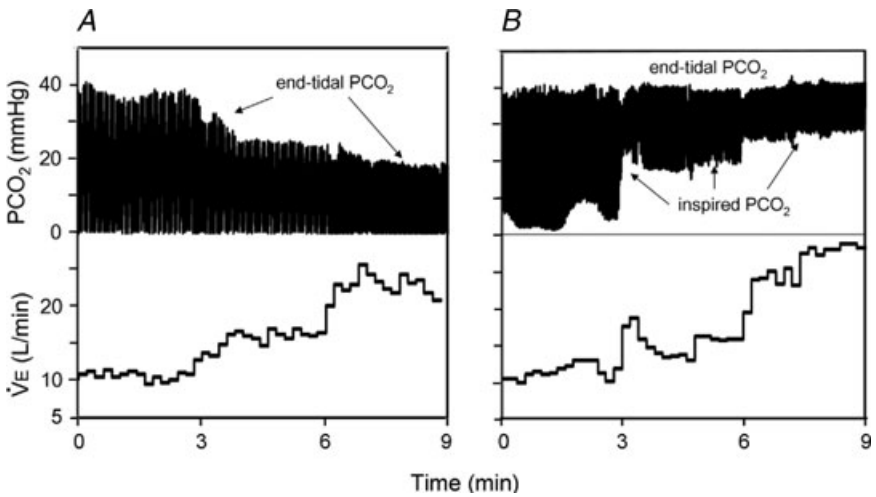

Figure 6. Data from a human subject to illustrate the effect of voluntary hyperventilation, without (*A*) and with maintenance of normocapnia (*B*) with the breathing circuit depicted in Fig. 6, on end-tidal P_{CO_2}
Lower panels show minute ventilation ($\dot{V}_E$) and upper panels show continuous capnograph traces. Peaks are end-tidal P_{CO_2} and troughs represent inspired P_{CO_2}. Note proportional increases in inspired P_{CO_2} as $\dot{V}_E$ increases; end-tidal P_{CO_2} remains unchanged, regardless of $\dot{V}_E$.

adjusted to match the patient's metabolic CO_2 production and controls the alveolar ventilation for CO_2. Arterial P_{CO_2} is therefore unchanged by any increase in ventilation, because any ventilation exceeding the O_2 flow is composed of 6% CO_2 in O_2, a mixture that does not contribute to a CO_2 diffusion gradient between capillary blood and the alveoli (Sommer *et al.* 1998; Somogyi *et al.* 2005; Fig. 6). However, it is the combined flow of O_2 and 6% CO_2 in O_2 that serves to wash out CO from the lungs, thereby clearing it from the blood.

The system is designed to be used in the field, but it cannot be readily improvised and requires deliberate preparation. It requires a customized breathing circuit or modification of available self-inflating bags, compressed CO_2-containing gas with specific pressure regulator and flow controller. Such tanks require care in storage or use in extreme cold because CO_2 liquefies readily when cold. Use of the system requires some clinical expertise or monitoring of end-tidal gas in order to set the fresh gas flow (O_2 or air) appropriately to attain an appropriate end-tidal P_{CO_2}. However, due to the benign nature of acute hypercapnia in adults (Potkin & Swenson, 1992; Ayas *et al.* 1998), as well as in children (Goldstein *et al.* 1990), when oxygenation is maintained, the fresh gas flow need not be exact and can be safely titrated to comfort or ventilatory response, or can be set according to guidelines based on approximate body weight.

Isocapnic hyperpnoea in practice

We suggest that the availability of a portable device to increase CO clearance would be a useful adjunct to current treatment of CO poisoning. It can be brought to the field to begin treatment immediately at the time of rescue and continue treatment during transportation to hospital. The same device can be applied to patients breathing spontaneously, as well as those requiring ventilatory assistance. Prior CO clearance at the site of rescue would make emergency air transport safer, should it be required. As normocapnia is maintained and there are no foreseeable risks, this treatment can be administered on the suspicion of CO poisoning. It would therefore provide the earliest possible treatment if CO poisoning is later confirmed, and nothing is lost if it is not. Carbon monoxide poisoning often occurs in clusters, and this treatment approach can be inexpensively and safely applied to all victims. Finally, early pulmonary CO clearance does not delay or preclude any other treatment, including subsequent treatment with hyperbaric O_2, if deemed necessary (Piantadosi, 2002; Weaver *et al.* 2002).

It is also noteworthy that isocapnic increases in alveolar ventilation with 21% O_2 would be as effective in eliminating CO as normobaric hyperoxia (Henderson & Haggard, 1920), yet avoid risk of the additional oxidative stress from hyperoxia. Furthermore, both hyperoxic and normoxic isocapnic hyperpnoea would also accelerate the clearance of any volatile hydrocarbons, including ethanol (Henderson, 1924; Hunter & Mudd, 1924), methanol, ingested poisons (Lemburg *et al.* 1979) and anaesthetic agents (Sasano *et al.* 2001; Vesely *et al.* 2003; Katznelson *et al.* 2008, 2010).

Summary

We believe we have now come full circle in the treatment of CO poisoning. At the beginning of the 20th century, carbogen proved to be an effective means of treating CO poisoning. Only relatively recently was it realized that it was not the CO_2 in carbogen but the increase in alveolar ventilation induced by the CO_2 that accelerated the clearance of CO. By then, however, rapid advances in the technology of positive-pressure ventilation and hyperbaric chambers overshadowed the old-fashioned approach using carbogen. Despite the initial enthusiasm for hyperbaric O_2 as the treatment for CO poisoning, the fact remains that hyperbaric O_2 facilities are expensive and their distribution around the world is poorly matched to the incidence and prevalence of CO poisoning. Even in wealthier urban areas, the inherent delays to initiate treatment make them clinically ineffective. The technical barriers to safely enable lung clearance of CO are low, making it feasible to provide for widespread availability of the means for early and rapid CO elimination. In any case, early pulmonary CO clearance does not delay or preclude any other treatment, including subsequent treatment with hyperbaric O_2.

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Potential conflict of interest

All of the authors have contributed to the development of the technology to increase the efficacy of pulmonary clearance of volatile hydrocarbons. Some related intellectual property (IP; US Patent No. 6,354,292) has been protected according to the guidelines of the Technology Development and Commercialization Office of the University Health Network (UHN). The UHN has licensed the IP to Thornhill Research Inc. (TRI), a UHN spin-off company. All of the authors own shares in TRI. J.F., L.F. and J.D. are also paid consultants to TRI.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

CO Model.zip.

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