

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 CO₂ and O₂ (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 CO₂; however, it was eventually realized that the increase in pulmonary ventilation was the predominant factor accelerating clearance of CO from the blood. The inhaled CO₂ 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 O₂. Now, a half-century later, there is accumulating evidence that hyperbaric O₂ is not efficacious, most probably because of delays in initiating treatment. We now also know that increases in pulmonary ventilation with O₂-enriched gas can clear CO from the blood as fast, or very nearly as fast, as hyperbaric O₂. Compared with hyperbaric O₂, 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 O₂.

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Background

At the turn of the 20th century, CO poisoning was treated by administering high concentrations of O₂ to increase the O₂ carried in the blood and, if necessary, ventilation was stimulated by adding CO₂. It was initially and mistakenly thought that patients asphyxiated to unconsciousness by CO had a total body deficit of CO₂ that was replenished by the inhaled CO₂ (Henderson *et al.* 1921). Furthermore, animal tests had shown that the addition of CO₂ to O₂ markedly increased the dissociation of carboxyhaemoglobin (COHb) and accelerated clearance of CO compared with using O₂ alone (Henderson & Haggard, 1920). Carbon dioxide was administered in concentrations of 5–10% in O₂, 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

by a deficit of CO₂ was rejected (Donald & Paton, 1955). Ventilatory stimulation by CO₂ 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 O₂ on the equilibrium (Haldane, 1895) $\text{COHb} + \text{O}_2 \rightleftharpoons \text{O}_2\text{Hb} + \text{CO}$ by administering the O₂ at hyperbaric pressures (Pace *et al.* 1950). Hyperbaric O₂ 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 O₂ 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 O₂ 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 O₂ 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 O₂ given the logistics of patient transport and chamber preparation, continue to show no benefit compared with normobaric O₂ (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 O₂ 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 O₂ 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

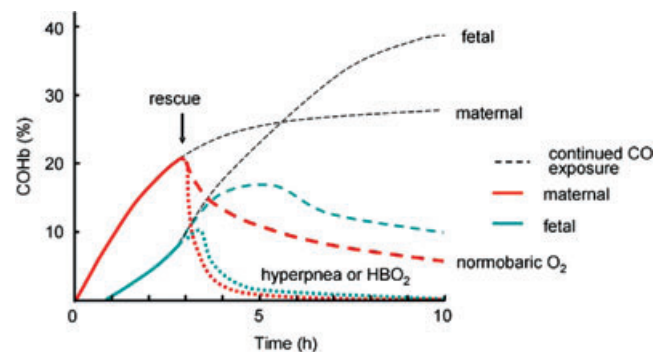


Figure 1. Schematic diagram illustrating the kinetics of [COHb] in mother (red) and fetus (teal) after 3 h exposure to CO and then rescue

Black dotted lines represent [COHb] at equilibrium; coloured dashed lines represent [COHb] with normobaric O₂ 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 O₂) 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 O₂ was considered an acceptable trade-off for the difficult logistics, increased expense and added delay in treatment. Despite little evidence of its value, hyperbaric O₂ has remained the mainstay of treatment for the last half a century.

Is normobaric oxygen a standard of care?

Even normobaric O₂ 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 O₂ 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 CO₂-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 O₂ produces only a very small increase in blood O₂ content that is carried in the plasma, where it is poorly soluble. If this small increase in blood O₂ content is accompanied by even a small reduction in tissue blood flow, the result can be a net reduction in organ O₂ delivery (Case *et al.* 1975; Rucker *et al.* 2002). Figure 2 illustrates that the administration of normobaric O₂, 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 O₂, where do we go from here?

Increased alveolar ventilation can be as effective as hyperbaric O₂

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 O₂. Previous studies (Henderson & Haggard, 1920) had concentrated on the

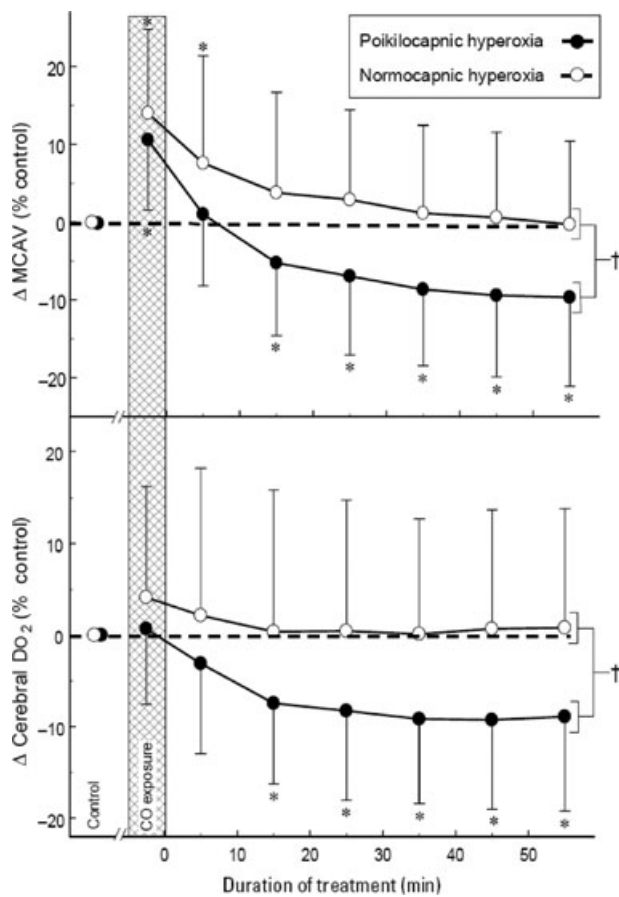


Figure 2. Effect of poikilocapnic and isocapnic normobaric O₂ treatment on cerebral O₂ delivery (DO₂) in CO-exposed human subjects

Fourteen human subjects were exposed on two separate occasions to CO until their [COHb] reached 10–12%. They were administered 100% O₂ with, and without, maintaining isocapnia. Blood O₂ delivery was calculated from arterial PO₂, arterial P_{CO_2} , haemoglobin saturation ($11 - [COHb]$), plasma O₂ 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 DO₂. (From Rucker *et al.* 2002, with permission from the publisher.)

relative efficacies of various mixtures of CO₂ in O₂ 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 CO₂ 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 O₂ (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 O₂ using a circuit that maintained normocapnia. Several findings from this study are of interest. First, the ventilatory response to normobaric O₂ (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

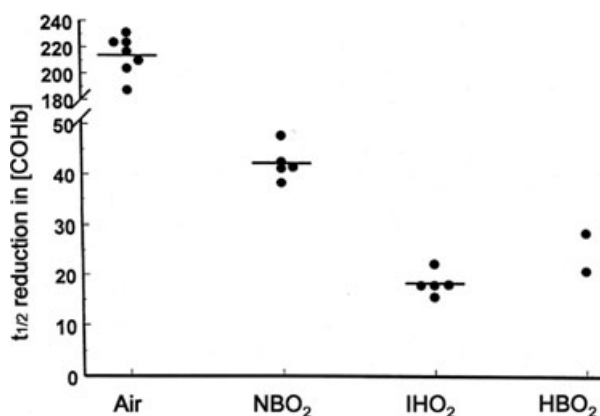


Figure 3. Elimination half-times for [COHb]

Five anaesthetized, intubated, spontaneously breathing dogs were exposed to CO until [COHb] reached ~70%. They were then administered, sequentially, room air (Air), normobaric O₂ (NBO₂) and then vigorously mechanically ventilated with O₂ while maintaining normocapnia (IHO₂). 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 O₂ at 3 atm (304 kPa). Isocapnic hyperpnoea resulted in a similar rate of [COHb] reduction to hyperbaric O₂ (HBO₂). 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.

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 O₂ (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_{CO₂}? 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 CO₂ due to ventilatory depression from severe CO poisoning or previously ingested drugs. As for those patients with an intact ventilatory response to CO₂, administration of CO₂ 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 CO₂ (Soley *et al.* 1941; Prisman *et al.* 2007) mean that

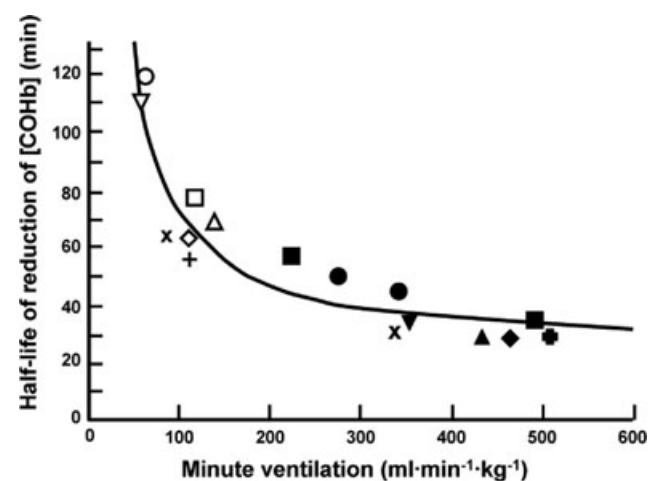


Figure 4. Half-time of COHb reduction versus minute ventilation in humans

Seven men were exposed to CO until [COHb] reached 10–12% on two separate occasions. On one occasion, subjects breathed 100% O₂ ('resting ventilation'). On the other occasion, subjects were administered 100% O₂ 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 O₂); 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 14.1 min⁻¹ for a 70 kg person. (From Takeuchi *et al.* 2000; reprinted with permission of the American Thoracic Society. Copyright © American Thoracic Society.)

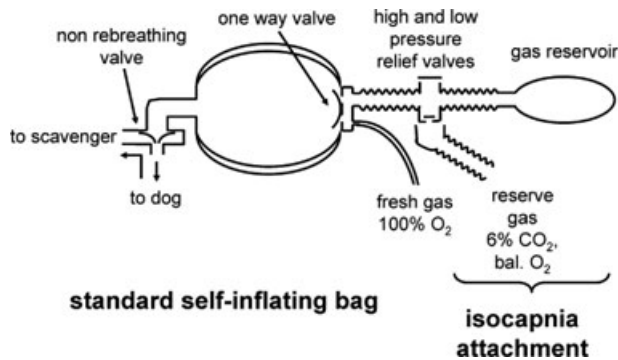


Figure 5. A self-inflating bag circuit suitable for spontaneous and controlled ventilation

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 CO₂ 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% CO₂. 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 CO₂ in an attempt to maintain normocapnia with hyperpnoea, one can administer CO₂ 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 O₂ 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% CO₂ in O₂ (Fig. 5). Any increase in minute ventilation above the O₂ flow is therefore supplied by the demand regulator (6% CO₂ in O₂). The O₂ flow is

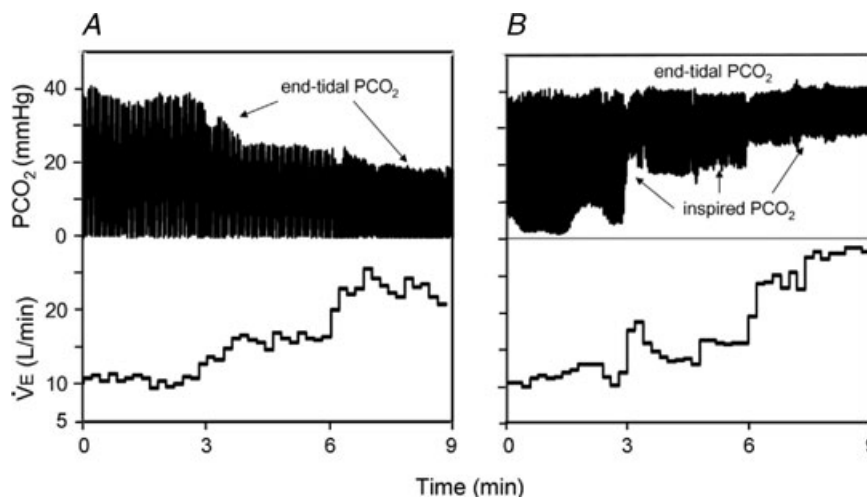


Figure 6. Data from a human subject to illustrate the effect of voluntary hyperventilation, without (A) and with maintenance of normocapnia (B) with the breathing circuit depicted in Fig. 6, on end-tidal P_{CO₂}

Lower panels show minute ventilation (\dot{V}_E) and upper panels show continuous capnograph traces. Peaks are end-tidal P_{CO₂} and troughs represent inspired P_{CO₂}. Note proportional increases in inspired P_{CO₂} as \dot{V}_E increases; end-tidal P_{CO₂} remains unchanged, regardless of \dot{V}_E .

adjusted to match the patient's metabolic CO₂ production and controls the alveolar ventilation for CO₂. Arterial P_{CO_2} is therefore unchanged by any increase in ventilation, because any ventilation exceeding the O₂ flow is composed of 6% CO₂ in O₂, a mixture that does not contribute to a CO₂ 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 O₂ and 6% CO₂ in O₂ 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 CO₂-containing gas with specific pressure regulator and flow controller. Such tanks require care in storage or use in extreme cold because CO₂ 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 (O₂ 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 O₂, if deemed necessary (Piantadosi, 2002; Weaver *et al.* 2002).

It is also noteworthy that isocapnic increases in alveolar ventilation with 21% O₂ 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 CO₂ in carbogen but the increase in alveolar ventilation induced by the CO₂ 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 O₂ as the treatment for CO poisoning, the fact remains that hyperbaric O₂ 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 O₂.

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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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