



The clinical toxicology of carbon monoxide

Des Gorman^{a,b,c,*}, Alison Drewry^{a,c}, Yi Lin Huang^a, Chris Sames^c

^a Department of Medicine, University of Auckland, Private Bag 92019, Auckland, New Zealand

^b The Liggins Institute, University of Auckland, Auckland, New Zealand

^c Royal New Zealand Naval Health Services, Naval Hospital, Auckland, New Zealand

Received 16 September 2002; received in revised form 24 October 2002; accepted 7 January 2003

Abstract

Carbon monoxide (CO) is a dangerous exogenous poison and an essential endogenous neurotransmitter. This gas when inhaled has an anaesthetic effect, which is poorly understood, but which may be fatal if compensatory mechanisms are exhausted, if cardiac oxygen (O₂) needs exceed myocardial oxygenation and/or if apnoea or asphyxia onsets. Although there is considerable evidence that hypoxia occurs late in CO poisoning, both the treatment of acutely poisoned people and environmental exposure limits are largely based on a hypoxic theory of toxicity. The significance of recent demonstrations of increased endogenous CO and NO production in neurons of animals exposed to exogenous CO, and of a related sequestration of leucocytes along the endothelium and subsequent diapedesis is also not fully understood, but may in part explain both acute and delayed deleterious effects of a CO exposure. Delayed brain injuries due to a CO exposure may be preventable by hyperbaric O₂. However, the ideal dose of O₂ in this context, if any, is unknown and other potential treatments need to be tested.

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Keywords: Carbon monoxide; Clinical toxicology; Exogenous poison

1. Introduction

A review of the clinical toxicology of carbon monoxide (CO) is justifiable for many reasons,

and especially because this ubiquitous, colourless, non-irritant, odourless environmental gas is often lethal when inspired, but at the same time it is an endogenous neurotransmitter (Barinaga, 1993;

Abbreviations: β-APP, Beta Alzheimer's precursor protein; BBF, Brain blood flow; CO, Carbon monoxide; COHb, Carboxyhaemoglobin; DNS, Delayed neurological sequelae; GCS, Glasgow coma scale; GFAP, Glial fibrillary acid protein; Hb, Haemoglobin; HBO, Hyperbaric oxygen; H and E, Haemotoxylin and Eosin; HO, Haeme oxygenase; Hx, History; kPa, kilopascals; LOC, Loss of consciousness; NBO, Normobaric oxygen; NLOC, No loss of consciousness; NMDA, *N*-methyl-D-aspartate; NNH, Number needed to harm; NNT, Number needed to treat; NO, Nitric oxide; NOS, Nitric oxide synthetase; O₂, Oxygen; OHb, Oxyhaemoglobin; P_IO₂, Partial pressure of inspired oxygen; PMNL, Polymorphonuclear leucocyte; RCT, Randomised controlled study; Rx, Treatment; TAF, Thionine and acid fusion; UPTD, Units of pulmonary toxic dose.

* Corresponding author. Tel.: +64-9-3737599x6261; fax: +64-9-3082379.

E-mail addresses: d.gorman@auckland.ac.nz, desmob@attglobal.net (D. Gorman).

Gorman and Runciman, 1991; Haley, 1998; Runciman and Gorman, 1993; Verma et al., 1993). Carbon monoxide is the most common lethal poison in every community yet studied, and accounts for more hospitalisations (50% attempted suicides and 33% occupational exposures in Australasia) than all other non-prescribed poisons combined (South Australian unpublished coronial data). Despite some form of treatment, more than 10% of survivors are left with a presumed brain injury (Juurlink et al., 2000; Myers et al., 1985). The onset of these injuries may be delayed for several days after the exposure. The assumed toxic mechanism of hypoxia secondary to hypoxaemia does not, by itself, explain much of the published *in vivo* and clinical data (Gorman et al., 2001, 2002; Langston et al., 1996; Ludbrook et al., 1992b; Mayesky et al., 1995; Meilin et al., 1996; Meyer-Witting et al., 1991; Thom et al., 1997). Nevertheless, the treatment of CO poisoned patients and environmental exposure limits are based on this theoretical toxicity (Juurlink et al., 2000; Kindwall, 1994).

This review of the hypotheses proposed to explain the toxicity of CO will be divided into hypoxic and cellular theories. This will be followed by a brief review of the management of people poisoned with CO in the context of evidence based best practice.

2. The hypoxic theory of carbon monoxide toxicity

Haldane (1896) proposed a hypoxic basis for CO toxicity in 1896. He argued that hypoxia would arise from the hypoxaemia that occurs when carboxyhaemoglobin (COHb) forms; this is still the most widely accepted explanation of CO toxicity (Kindwall, 1994). Thirty-one years later, his son reported an experiment, which demonstrated that CO had a mortal toxicity that did not appear to be related to haemoglobin (Hb) (Haldane, 1927).

There are also other strong *in vivo* and clinical arguments against a paramount hypoxic hypothesis for CO toxicity.

In vivo experiments in many different animal models and clinical studies have produced variable

results, from isolated white matter injury to discrete apoptosis, to diffuse cortical atrophy (Gale et al., 1999; Ginsberg et al., 1974; Gorman et al., 2001; Okeda et al., 1981; Piantadosi et al., 1997; Prockop and Naidu, 1999; Thom et al., 2000). The extent to which these results are compatible with a hypoxic injury is variable and in some animal studies the effect of CO has been shown to be independent of COHb formation and/or hypoxia (Ludbrook et al., 1992b; Meilin et al., 1996, 1998; Thom et al., 1997). Although plasma lactate levels do increase in animals exposed to CO (Penney and Chen, 1996), the lactate does not appear to originate in the brain (Langston et al., 1996). In addition, increased plasma levels of oxidised proteins seen in rats after a CO exposure are neither directly related to hypoxic stress from COHb formation nor significantly influenced by circulating platelets or polymorphonuclear leucocytes (PMNL), but are reduced by nitric oxide synthetase (NOS) blockade (Thom et al., 1997).

Studies in anaesthetised rabbits and in awake sheep have shown that hypoxia cannot explain the early anaesthetic or cortical evoked response suppressant effects of CO (Gorman et al., 2001, 2002; Langston et al., 1996; Ludbrook et al., 1992b; Meyer-Witting et al., 1991). Hypoxaemia, whether caused by an inert diluent or CO, causes an increase in heart rate, cardiac output and brain blood flow (BBF) that maintains oxygen (O₂) delivery to the brain (see Figs. 1 and 2). As cited above, this increase in BBF occurs independently of COHb formation and/or tissue hypoxia (Mayesky et al., 1995; Meilin et al., 1996). However, it does appear to be regulated and not a simple vasodilatory response to CO and/or nitric oxide (NO) as O₂ delivery to the brain is near-perfectly maintained in rabbits and sheep exposed to CO (see Figs. 1 and 2) (Langston et al., 1996; Ludbrook et al., 1992b). Red blood cells are released into the circulation, presumably from the spleen, to further increase O₂ delivery (Gorman et al., 2001). Although O₂ dissociates from Hb at lower O₂ tensions in the presence of COHb, cerebral arterio-venous O₂ extraction and BBF data were used to show that the uptake of O₂ by the brain during a narcotic CO exposure in previously awake sheep was adequate for normal

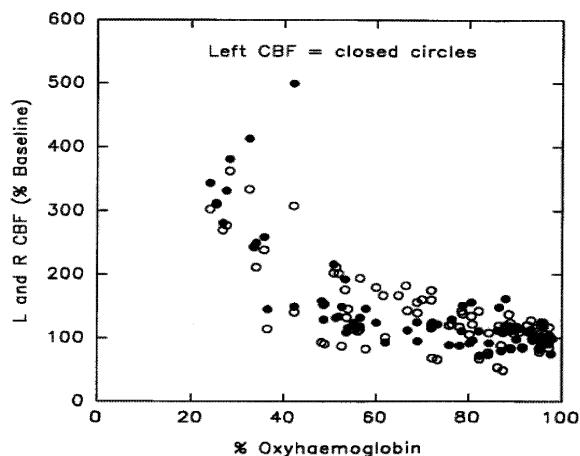


Fig. 1. Left and right cerebral hemispheric blood flow (H_2 -clearance) versus oxyhaemoglobin concentration in rabbits made hypoxaemic by either dilution of inhaled air with nitrogen or carbon monoxide (Ludbrook et al., 1992b).

function (Langston et al., 1996). Nevertheless, despite this maintenance of O_2 delivery and uptake, and in the absence of any biochemical markers of neuronal hypoxia, evoked responses are inhibited in anaesthetised rabbits and awake sheep are narcotised both apparently and electrophysiologically (see Fig. 3). Hypoxia is only seen in these animals when COHb levels are very high (> 70%) and the cardiovascular and cerebrovascular homeostatic response is overwhelmed (see Fig. 1). The BBF autoregulatory response to hypoxaemia in general and to CO specifically cannot only be overwhelmed by decreasing oxyhaemoglobin concentration (OHb) (Langston et al., 1996), but also by sufficiently high doses of CO to cause episodes of spontaneous brain depolarisation (Mayesky et al., 1995) and by induced cortical spreading depression (Meilin et al., 1998). The autoregulation is also lost in aged rats (Mendelman et al., 2000). Such an aging effect, along with the increasingly compromised cardiovascular and cerebrovascular function that is seen with increasing age and that will limit any BBF autoregulation, may explain the observation that age is a risk factor for poor outcome in CO poisoned people (Weaver et al., 2002). The significance of this autoregulation in CO poisoning underpins the

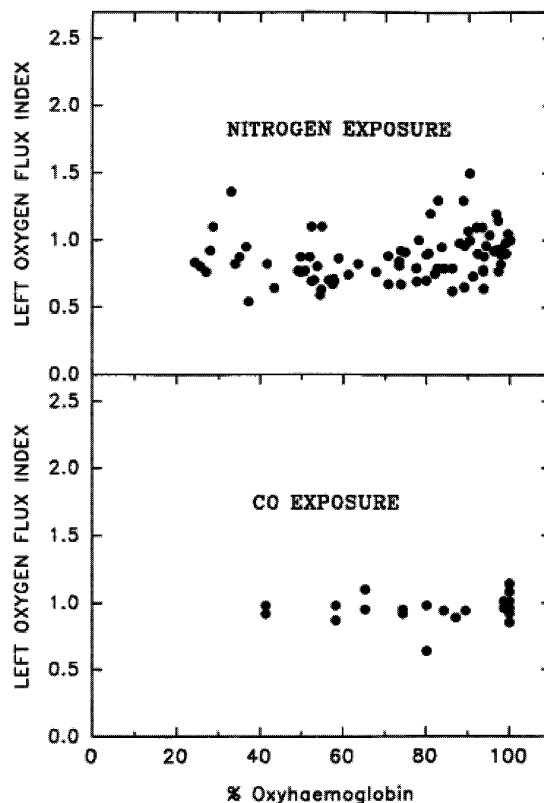


Fig. 2. Left cerebral hemispheric oxygen flux (blood flow \times oxygen content) versus oxyhaemoglobin concentration in rabbits made hypoxaemic by either dilution of inhaled air with nitrogen or carbon monoxide (Ludbrook et al., 1992b).

concern that we have about the *in vivo* confusion of the effect of CO alone and that of an interaction of CO and ischaemia. It is our opinion that this is a common feature of many *in vivo* models of CO poisoning. To illustrate our concern, brain lesions seen in sheep after an exposure to CO are more concentrated ipsilaterally in the hemisphere that is on the same side of the body as any carotid artery cannulation (Gorman et al., 2001). Some caution is needed in the interpretation of the *in vivo* data for the following reasons:

- First, anaesthesia has been usual in these studies and this will affect cerebrovascular behaviour and obscure the behavioural effects of the poison (Gorman et al., 2001, 2002; Ludbrook et al., 1992a).

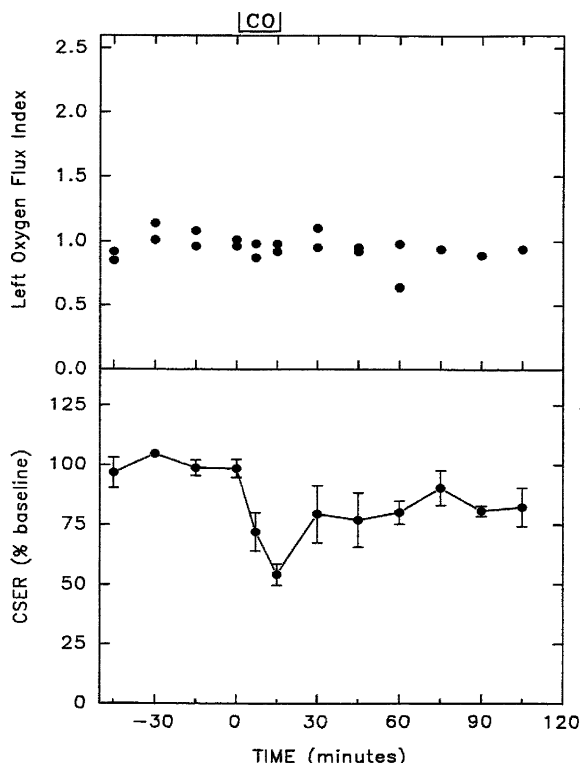


Fig. 3. Left cerebral hemispheric oxygen flux (blood flow \times oxygen content) and the voltage amplitude of a cortical somatosensory evoked response (CSER) before, during and after a 15 min exposure to carbon monoxide in air (Ludbrook et al., 1992b).

- Second, as cited above, many studies have probably caused a combined CO-ischaemic injury and such an interactive insult is very different from that of CO alone (Gorman et al., 2001). This is not surprising given the maintenance of O_2 delivery to the brain, which occurs during and after an exposure to CO as a consequence of a sequential increase in heart rate, cardiac output and BBF, and that has been reported in rats, anaesthetised rabbits and awake sheep (see Figs. 1 and 2) (Gorman et al., 2001, 2002; Langston et al., 1996; Ludbrook et al., 1992b; Mayesky et al., 1995; Meilin et al., 1996, 1998; Meyer-Witting et al., 1991; Penney and Chen, 1996). It is likely that this protective BBF autoregulatory effect is mediated by NO (Meilin et al., 1996).

- Third, there has been a wide variety in the employed species, CO administration protocols and outcome measures.

It is also difficult to reconcile clinical observations of CO poisoned patients with a paramount hypoxic toxicity (Gorman et al., 1992; Gorman and Runciman, 1991; Juurlink et al., 2000; Myers et al., 1985; Runciman and Gorman, 1993). The quality of health outcomes does not correlate well with the measured COHb levels. Poisoned patients usually have normal blood gases, are normotensive and have few if any systemic markers of hypoxia. Radiological and pathological findings are often not well explained by hypoxia alone.

However, as is the case for the in vivo studies, caution is needed in interpretation (Gorman et al., 1992; Gorman and Runciman, 1991; Juurlink et al., 2000; Myers et al., 1985; Runciman and Gorman, 1993). Most studies are not controlled. Those controlled studies have been small and most have been variously but significantly flawed (see Table 1). Almost half of all poisonings are suicide attempts. Other poisons are often used simultaneously and long-term recovery is complicated by the original mental health disorder. Many patients have a super-imposed hypoxic injury due to asphyxia and/or apnoea. The time from exposure to treatment varies and O_2 is used to a variable extent in the acute resuscitation. Pre-morbid neuropsychometric data do not exist, and it is probable that most outcome surveys have over-estimated the extent of any brain injury and have mistaken co-morbidities for such injury.

3. The cellular theories of carbon monoxide toxicity

As cited above, JBS Haldane (1927) demonstrated that CO had a mortal toxicity that appeared to be independent of Hb. Subsequently, proposed toxic mechanisms to account for this observation include binding to mitochondrial cytochromes, myoglobin, and to non-specific absorption onto catalyst surfaces (Gorman and Runciman, 1991; Piantadosi, 1987; Runciman and Gorman, 1993).

Table 1
Comparison of randomised controlled studies of HBO versus NBO in CO Poisoning

Authors	Study design	Protocol	Comments	NNT ^a
Raphael et al. (1989)	Non-blinded RCT	HBO at 202 kPa	Non-blinded	LOC 50
	Four groups: two with, two without loss of consciousness (LOC) LOC control (<i>N</i> = 127) HBO/NBO 203 kPa, 540 UPTD LOC (<i>N</i> = 125) HBO/NBO/HBO 203 kPa, 840 UPTD NLOC control (<i>N</i> = 148) NBO 101 kPa, 360 UPTD NLOC (<i>N</i> = 159) HBO/NBO 203 kPa, 540 UPTD Delay to treatment < 12 h (av. 6 h) Follow-up at 1 month	HBO 2 h, NBO 4 h HBO 2 h/NBO 4 h/HBO 2 h NBO 6 h HBO 2 h, NBO 4 h	Many included with very mild poisoning Both LOC groups had HBO	NLOC 50
Thom et al. (1995)	Non-blinded RCT	HBO 282 kPa for 30 min then 2.0ATA for 90 min preceded by NBO, av. 2.1 h NBO for av. 4.2 h	Excluded if Hx of loss of consciousness or ECG changes Non-blinded	4
	HBO (<i>N</i> = 30) 284 kPa, av. 338 UPTD NBO (<i>N</i> = 30) 101 kPa, av. 252 UPTD Delay to treatment < 6 h (av. 2 h) Follow-up at 1 and 3 months			
Ducasse et al. (1995)	Single-blinded RCT	HBOT 252 kPa 2 h, then NBO 100% 4 h then 50% 6 h	Small sample	2, 2 h post Rx
	HBO (<i>N</i> = 13) 253 kPa, 620 UPTD	NBO 100% 6 h then 50% 6 h	Patients/staff not blinded to treatment	3, 12 h post Rx
	NBO (<i>N</i> = 13) 101 kPa, 360 UPTD Delay to treatment < 2 h Follow-up at 2 and 12 h		No long-term follow-up Surrogate outcomes rather than DNS measured GCS < 12 excluded	
Mathieu et al. 1996	Non-blinded RCT	HBOT 2.5ATA 90 min	Interim report only	33 at 1 months
	HBO (<i>N</i> = 299) 253 kPa, 285 UPTD	NBO 100% 12 h	No details of outcome measures or dropout rate	18 at 3 months
	NBO (<i>N</i> = 276) 720 kPa, 101 UPTD		No sham treatment No details of randomising or blinding	33 at 6 months 143 at 12 months

Table 1 (Continued)

Authors	Study design	Protocol	Comments	NNT ^a
	Delay to treatment < 12 h Follow-up at 1, 3, 6 and 12 months			
Scheinkestel et al. (1999)	Double-blinded RCT	HBOT 282 kPa 60 min × 3 over 72 h, NBO (av. 60%) between treatments. This repeated by 28% of group	Unusually high oxygen doses	–17 post-Rx
	HBO (N = 104) 284 kPa, 1879 UPTD	NBO (100%) 100 min in chamber × 3 over 72 h with 60% NBO between treatments. This repeated by 15% of group	Only 46% follow-up at 1 month	–21 at 1 months
	NBO (N = 87) Sham in multiplace 101 kPa, 1423 UPTD Three days of oxygen via non-occlusive mask between HBO/Sham HBO treatments		<i>t</i> -Scores calculated on age/education-based norms (but unknown pre-morbid state) Jadad score 5/5, but Cochrane review states 'high likelihood of spurious statistical significance'	
	Delay to treatment av. 7.1 h Follow-up post treatment and at 1 month			
Weaver et al. (2002)	Double-blinded RCT	HBOT 303 kPa 50 min then 2.0ATA 60 min at 0 h, followed by 2.0ATA 2 h × 2 at 6 and 12 h	Small sample size	5 at 6 weeks
	HBO (N = 25) 304 kPa, 941 UPTD	'NBO' 116 kPa 145 min at 0 h, then 116 kPa air for 2 h × 2 at 6 and 12 h		6 at 6 months
	NBO (N = 25) Sham in monoplace 116 kPa, 174 UPTD			7 at 12 months
	HBO (N = 76) 304 kPa, 941 UPTD			
	NBO (N = 76) Sham in monoplace 116 kPa, 174 UPTD			
	Delay to treatment < 23 h Follow-up post treatment and at 2 and 6 weeks			
Myers et al. (1985)	HBO (N = 131) 284 kPa, 164 UPTD	HBOT 282 kPa 46 min	Not randomised or blinded	8
	NBO (N = 82) 101 kPa, 240+UPTD	NBO 100% 4 h (or more)	Biased control group	
	Delay to treatment av. 30 min Follow-up at 1–21 days post treatment and 6–12 months			

Accurate figures for NNH (number needed to harm) could not be calculated from the available data.

^a NNT, number needed to treat.

However, relevant cellular enzymes such as cytochrome *c* ($a-a_3$) have a greater affinity for O_2 than CO, in contrast to Hb, such that limited CO–cytochrome binding may occur in the absence of tissue hypoxia (Piantadosi, 1987). Even allowing for the usually low levels of mitochondrial O_2 , this argument has been used to discount significant intra-cellular CO poisoning; but, for reasons discussed below, this disregard may be inappropriate. Thom has proposed one hypothesis that may explain the delayed effects of CO poisoning (Ischiropoulos et al., 1996; Thom, 1993; Thom et al., 1994, 1997, 1999, 2001). He hypothesised that CO activates PMNL's, which diapedese and cause brain lipid peroxidation. Further, he noted that CO affects platelet scavenging of NO, which in turn will interfere with PMNL binding to endothelial cells, such that the diapedesis will be delayed until after the CO is withdrawn. That is, this phenomenon can explain the delayed but not the anaesthetic effects of CO. The process of PMNL diapedesis and brain lipid peroxidation is inhibited by 303 kPa of O_2 , but not at 101 kPa. This might explain some of the clinical reports that delayed brain injury is prevented by hyperbaric O_2 (HBO) (Myers et al., 1985; Runciman and Gorman, 1993; Weaver et al., 2002). In the most recent controlled randomised clinical study reported, and using an intention to treat analysis, the numbers needed to treat (NNT) for HBO versus normobaric O_2 (NBO), to prevent such a delayed effect 6 weeks, 6 months and 1 year after the exposure were 4.76, 5.88 and 6.66, respectively (Weaver et al., 2002). Such data are in conflict with an Australian study that showed a negative NNT of 21 1-month after treatment with HBO (Scheinkes et al., 1999) and with a French controlled study that suggested only short-term benefit for HBO in the context of preventing delayed neuropsychiatric sequelae (Mathieu et al., 1996); the NNT in the latter study increased from 18 at 3 months, to 33 at 6 months and to 143 at 12 months. It is most noteworthy that all the controlled studies published to date, with the probable exception of the most recent (Weaver et al., 2002), have been sufficiently flawed to make their utility low (see Table 1) (Juurink et al., 2000).

Since Thom's original observations (Thom, 1993; Thom et al., 1994), more data has been published in support of and to clarify this mechanism of delayed injury. First, CO has been shown to induce both neuronal and glial NOS and haeme oxygenase (HO) and hence to increase intracellular levels of both NO and CO (Gorman et al., 2002; Ischiropoulos et al., 1996; Thom et al., 1999). Second, CO not only increases NO levels, but also is responsible for the potent oxidant, peroxynitrite, being deposited in vascular walls and throughout the brain parenchyma; this is probably secondary to PMNL sequestration in the microvasculature, and is seen together with xanthine oxidase formation and brain lipid peroxidation, all of which are prevented to some extent by NOS blockade (Ischiropoulos et al., 1996; Thom et al., 1999, 2001). Third, these latter effects are not influenced significantly by neutropenia or thrombocytopenia (Thom et al., 1999). Fourth, the CO-induced PMNL adherence to endothelium seen in rats, which becomes apparent about 18 h after the exposure and hence some time after the blood brain barrier is first seen to be damaged (Thom et al., 1999), is induced by qualitative changes in platelet activating factor (Thom et al., 2001). The failure of a pilot study in sheep to show benefit for lignocaine in CO poisoned sheep is surprising in this context (Gorman et al., in press and Mitchell, 2001).

Other researchers have argued that CO has direct psychiatric effects by deranging dopaminergic and serotonergic neural function (Hiramatsu et al., 1994; Muraoka et al., 1998). This is unaffected by *N*-methyl-D-aspartate (NMDA) receptor ion channel complex blockade (Hiramatsu et al., 1994), although the latter largely prevents CO-induced hippocampal cortical injury in rats and mice (Ishimaru et al., 1992; Penney and Chen, 1996). Such hippocampal neurodegeneration and the perhaps related learning deficits in CO poisoned mice are variously affected by neuroactive steroids (Tangui et al., 2000).

The final major cellular theory relates to the role of CO as an endogenous neurotransmitter (Barinaga, 1993; Haley, 1998; Verma et al., 1993). Some neurons are rich in HO and some neural tract function is dependent on CO production. The

suggestion then is that injury by inhaled CO may be caused by an excess of neural functions normally regulated by CO and/or by agonist antagonism of neuronal function normally under NO regulation (Kostoglou-Athanassiou et al., 1998).

Narcotic doses (1% in air) of CO administered to awake sheep for up to 2 h, induces anaesthesia (Gorman et al., 2001, 2002). The histological and immunochemical outcome in the brains of these sheep were compared 5–14 days later with control sheep, which were not exposed to CO but were matched for process in every other way. The CO exposed sheep showed a statistically significant increase in periventricular white matter infarcts, with glial activation about these infarcts and some axonal dysfunction (see Fig. 4). Very surprisingly, there was no evidence of neuronal death or apoptosis, but clear evidence of neuronal and glial activation of HO-1 and -2 and NOS-1 and -2, but not of NOS-3, which is endothelial (see Fig. 4).

While much of the last of these observations cannot be currently explained other than as a stress response (Sharma et al., 1998), to some degree the significance of any neuronal induction of HO and NOS is apparent. Most importantly, the cellular theories of CO poisoning need to be revisited, as intracellular NO and presumably CO will rise significantly (Ischiropoulos et al., 1996; Meilin et al., 1996; Thom et al., 1997, 1999). As cited above, the cellular theories have been discounted to date on the basis of the relative affinities of O₂ and CO to mitochondrial cytochromes, which favours O₂ binding (Piantadosi, 1987). This is clearly not the case for guanylyl cyclase, which binds either CO or NO to produce cyclic-GMP (Barinaga, 1993; Haley, 1998; Verma

et al., 1993). The potential for cellular dysfunction then is apparent.

It is even possible that the anaesthetic effect of CO is relatively harmless as is the case for most other general anaesthetics. The sheep studies cited above would support this argument (Gorman et al., 2001). The difference between these sheep and other *in vivo* models and people poisoned with CO may be explained variously by the following:

- First, the sheep preparation avoided any ischaemia and other disruption of cerebrovascular behaviour and did not combine the CO exposure with an anaesthetic, which is the case for most other *in vivo* work. Nevertheless, a greater concentration of white matter infarcts was still found in the brain hemisphere ipsilateral to the carotid artery cannulated for monitoring. One sheep showed impaired BBF after surgical preparation and when that sheep was exposed to CO, the resulting brain injury was much worse than for any other sheep studied.
- Second, there may be species differences in the manner in which BBF is maintained and/or in which red cells are released into the circulation. However, such effects have been reported in rats, rabbits and sheep (Gorman et al., 2001, 2002; Ischiropoulos et al., 1996; Langston et al., 1996; Ludbrook et al., 1992b; Mayesky et al., 1995; Meilin et al., 1996, 1998; Meyer-Witting et al., 1991; Penney and Chen, 1996) and similar results have been cited in cats and monkeys (Ginsberg and Myers, 1974; Okeda et al., 1981).
- Third, the sheep airway was maintained during the CO-induced anaesthesia.

Our hypothesis here is that acute brain injury in CO exposed people may largely arise from hypoxia

Fig. 4. Representative samples of CO-induced white matter damage and HO-1 immunochemistry in the sheep brain 5 days post CO exposure (control sheep panels on the left) (Gorman et al., 2001; Gorman et al., *in press*). (A–B) H and E staining showing normal brain white matter (A) and peri-ventricular white matter micro-infarction (arrows) and gliosis after a CO exposure (B). (C–D) GFAP immunostaining of glial activity showing greater activity (about the infarcts cited above) in brain white matter after a CO exposure (D). (E–F) β -APP immunostaining showing positive stained and hence damaged axons (about the infarcts cited above) in brain white matter after a CO exposure (F). (G–H) HO-1 immunostaining showing a greater frequency of cells demonstrating HO-1 activity in brain white matter (H) and cortex (insert) after a CO exposure. Scale bar: 1 cm = 25 μ m.

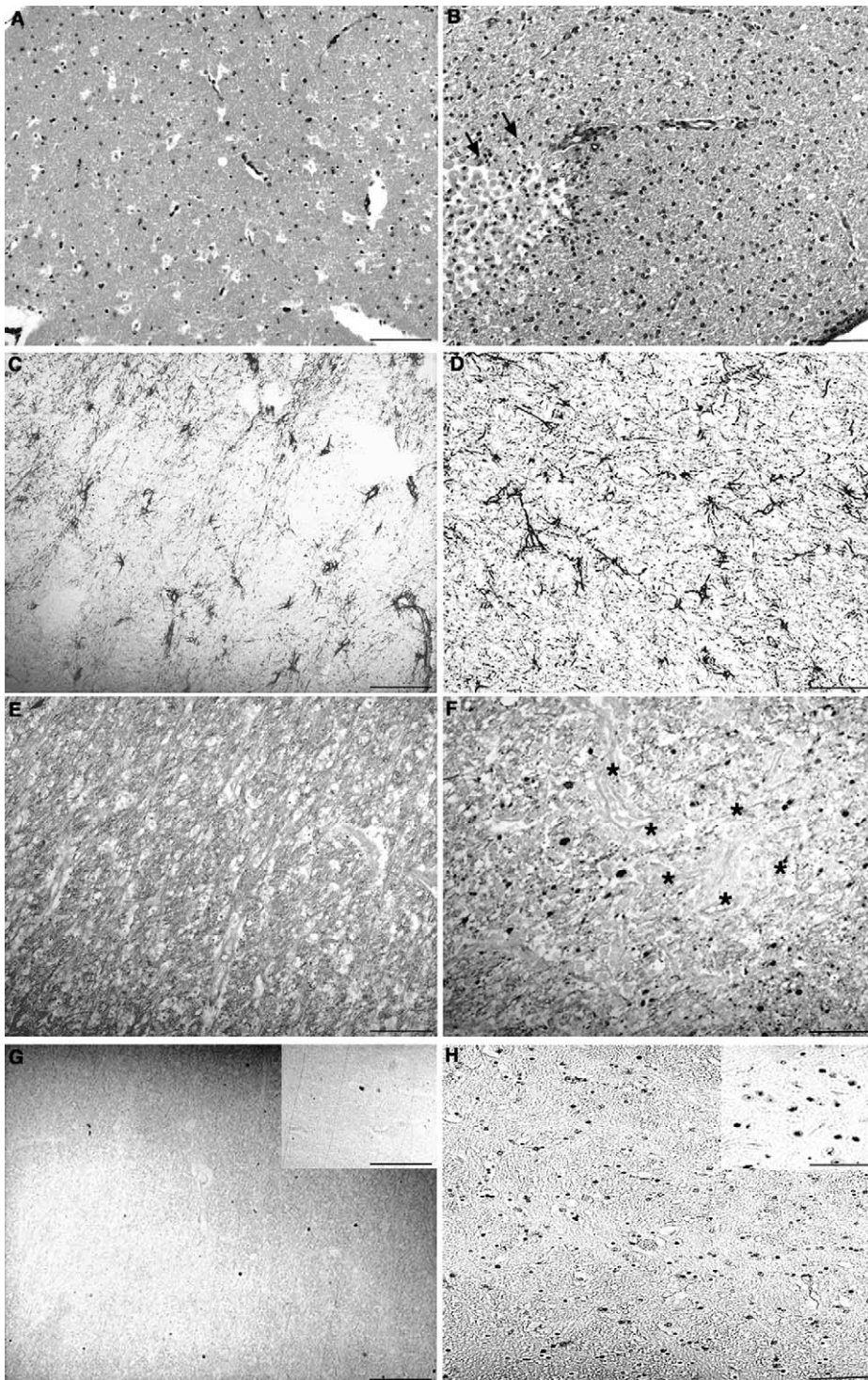


Fig. 4

due to either asphyxia and apnoea (during what is essentially an uncontrolled general anaesthetic exposure) and aspiration of vomitus, or to failure of the cerebrovascular compensation for the CO-induced hypoxaemia. The latter will be accelerated by myocardial disease and ischaemic heart disease, by cerebrovascular arteriosclerosis, which will impair reactivity, and compounded by the use of other brain active substances such as tri-cyclic antidepressants and alcohol as part of a suicide attempt and by concurrent exposure to fume such as hydrogen cyanide in a house fire. We also believe that Thom's PMNL theory (Ischiropoulos et al., 1996; Thom, 1993; Thom et al., 1994, 1997, 1999, 2001) at least in part explains any delayed neural injury; a similar mechanism has been shown to account for brain injury after arterial air embolism (Helps and Gorman, 1991). This has therapeutic implications (Mitchell, 2001). However, we are cognisant of the strong relationship between recovery after a head injury and pre-morbid factors such as depression, emotional coping skills and work satisfaction (Kushner, 1998), and hence are uncertain as to the extent to which the delayed neuropsychological sequelae of CO are due to brain injury and the extent to which they are a reaction to an acute threat to health and hospitalisation, with consequent illness beliefs (Pilowsky, 1997). It is also noteworthy that many CO exposures in first world countries are suicide attempts (unpublished South Australian Coronial data). A control group of non-CO exposed acutely hospitalised patients, both for and not for suicide attempts is clearly necessary in any longitudinal study of CO poisonings.

4. The management of CO poisoned patients

Most attention in the treatment of CO poisoned people has been on the breathing of 100% O₂ to reduce the half-life of COHb (Gorman and Runciman, 1991; Juurlink et al., 2000; Myers et al., 1985; Runciman and Gorman, 1993). However, COHb is not toxic in itself (Goldbaum et al., 1975; Orellano et al., 1976), and brain hypoxia is probably not a feature of CO poisoning until

either cardiovascular homeostasis is exhausted (see Fig. 1) and/or asphyxia or apnoea onsets (Gorman et al., 2001, 2002; Langston et al., 1996; Ludbrook et al., 1992b; Mayesky et al., 1995; Meilin et al., 1996, 1998; Meyer-Witting et al., 1991; Penney and Chen, 1996). Not surprisingly then, an ideal dose of O₂, if it exists, has neither been identified by these clinical studies (Juurlink et al., 2000) nor can it be derived from other clinical situations and/or from in vitro and in vivo data. The following three observations illustrate the reason for the latter comment:

- First, the half-life of COHb varies widely between individuals and is inspired O₂ tension (P_IO₂) dependent (Sasaki, 1975; Smart, 2002; Weaver et al., 2000), varying from several hours at 21 kPa to much less than an hour at 101 kPa and especially at 282 kPa.
- Second, in a large German study of traumatic brain injury (Holbach and Caroli, 1974), brain function and metabolism was enhanced at a P_IO₂ between 101 and 151 kPa, but were progressively worse between 202 and 252 kPa.
- Third, Thom (1993) has shown that the delayed PMNL diapedesis and subsequent lipid peroxidation that is seen in rats after a CO exposure, is inhibited if they breathe a P_IO₂ of 303 kPa, but not at 101 kPa. Clearly, two points on a dose continuum do not demonstrate the nature of the relevant dose response relationship and the extrapolation of these rodent data directly to the human experience should be cautious.

This uncertainty about dose is not to argue that breathing O₂ is not useful for the following reasons:

- First, reducing the half-life of COHb and accelerating the clearance of body stores of CO is intuitively worthwhile.
- Second, many patients will be hypoxic because of asphyxia and apnoea.
- Third, and as cited above, Thom (1993) has shown that HBO, but not NBO will inhibit the delayed PMNL diapedesis and subsequent lipid peroxidation that occur after a CO exposure.

The latter is consistent with the data presented by a Salt Lake City research group (Weaver et al., 2002), in which and again as cited above, the NNT for HBO over NBO in preventing delayed neural sequelae both 6 weeks and 1 year after the exposure was 4.76 and 6.66, respectively. However, a Cochrane Collaboration Review of earlier controlled randomised studies could not show any sustained benefit for HBO in this context (Juurlink et al., 2000). Several conclusions can be made from this Cochrane review:

- First, the controlled studies reported are, with the probable exception of the Salt Lake City study (Weaver et al., 2002), flawed and of low utility (Ducasse et al., 1995; Mathieu et al., 1996; Raphael et al., 1989; Scheinkestel et al., 1999; Thom et al., 1995). We have summarised the studies in Table 1.
- Second, the Cochrane review itself is internally inconsistent. For example, the Australian study (Scheinkestel et al., 1999) was given a Jadad rating of 5 by the Cochrane reviewers (Jadad et al., 1996), despite their recognition of a statistical approach that made consequent error inevitable.
- Third, the Cochrane reviewers did not cite what is arguably the most impressive clinical study published to date (Myers et al., 1985), which while it was not randomised and has many features that are not well described, had a biased control group that was selected by a clinical triage of such factors as COHb levels, and clinical and neuropsychometric status. This study is also summarised in Table 1 and shows not only an apparent strong advantage for HBO over NBO, but also that conventional triage techniques do not identify those patients likely to develop delayed neural sequelae. The latter may even support the argument cited above that these sequelae may be largely independent of any acute CO-induced brain injury per se.
- Fourth, the studies have used such different doses of HBO and NBO that any compilation of data is impossible. We have used an established biological marker of O₂ dose (Bardin and Lambertson, 1970) to quantify both HBO and

NBO doses in Table 1. The concern here is that some physicians have elected to rely on NBO to treat CO poisoned patients, as a consequence of the Australian study (Scheinkestel et al., 1999), but are using a dose of NBO very dissimilar to that used by the researchers.

- Fifth, only the Australian (Scheinkestel et al., 1999) and the Salt Lake City (Weaver et al., 2002) studies used a sham treated control group, although the first of these studies also lost more than half of all subjects to follow up. The explanation offered by the authors that this was accounted for by doubling the number of patients recruited is not a satisfactory response.

In conclusion, while we do not agree with some aspects of the Cochrane review (Juurlink et al., 2000), we do agree with their conclusions. It follows that data do not exist to establish evidence-based best practice. This is also true for patient selection. In contrast to the high risk factors identified in the Salt Lake City study (any one of the following: age > 50 years; COHb > 25%; a history of loss of consciousness; evidence of metabolic acidosis) (Weaver et al., 2002), a similar triage failed to identify those likely to suffer delayed neuropsychological sequelae in the biased control group study cited above (Myers et al., 1985). Medico-legal issues may even predominate in clinical decision-making and the latter may pay attention to this biased control group study data (Myers et al., 1985).

Also as cited above, the observation that CO causes PMNL diapedesis, that this may explain the CO-induced delayed brain injury and that this is preventable in vivo by HBO but not NBO (Thom, 1993) has therapeutic implications, not only for HBO but also for chemical interventions. A similar mechanism of brain injury occurs in cerebral arterial gas embolism (Helps and Gorman, 1991). Such emboli are probably responsible for much of the brain injury commonly seen after open-heart surgery and a lignocaine infusion has been shown to significantly reduce the frequency and severity of such injury in cardiac surgical patients (Mitchell et al., 1999; Wang et al., 2002). The rationale for lignocaine in this context is well established both in vitro and in vivo (Mitchell, 2001). However, and

as cited above, a pilot study in sheep suggests that the interaction of lignocaine and CO may increase the likelihood of white matter infarcts, such that other potentially therapeutic agents need to be tested (Gorman et al., in press).

In the interim, while the incidence and often poor outcome of CO poisoning is well recognised, and although the biology of CO is increasingly understood, the toxicology of the gas is mysterious and no data exist to establish best practice for managing poisoned patients. The potential for research is clear and urgently needed.

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