Normocapnia Improves Cerebral Oxygen Delivery During Conventional Oxygen Therapy in Carbon Monoxide–Exposed Research Subjects

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Study objective: We determine whether maintaining normocapnia during hyperoxic treatment of carbon monoxide–exposed research subjects improves cerebral oxygen delivery.

Methods: This experiment used a randomized, single-blinded, crossover design. We exposed 14 human research subjects to carbon monoxide until their carboxyhemoglobin levels reached 10% to 12%. We then treated each research subject with 60 minutes of hyperoxia with or without normocapnia. Research subjects returned after at least 24 hours, were reexposed to carbon monoxide, and were given the alternate treatment. Relative changes in cerebral oxygen delivery were calculated as the product of blood oxygen content and middle cerebral artery velocity (an index of cerebral blood flow) as measured by transcranial Doppler ultrasonography.

Results: Maintaining normocapnia during hyperoxic treatment resulted in significantly higher cerebral oxygen delivery compared with standard oxygen treatment (P<.05; 95% confidence interval at 60 minutes 2.8% to 16.7%) as a result of the prevention of hypocapnia-induced cerebral vasoconstriction and more rapid elimination of carbon monoxide due to increased minute ventilation.

Conclusion: If severely poisoned patients respond like our research subjects, maintaining normocapnia during initial hyperoxic treatment of carbon monoxide poisoning may lead to increased oxygen delivery to the brain. Determining the effect of such a change in conventional treatment on outcome requires clinical studies.

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INTRODUCTION

Carbon monoxide inhalation is the leading cause of fatal poisoning in the industrialized world.[1] In the United States, there are 40,000 emergency department visits per year resulting from carbon monoxide poisoning[2] and an estimated 3,500 to 4,000 deaths.[3] An important mechanism of carbon monoxide toxicity is tissue hypoxia resulting from the displacement of oxygen from hemoglobin by carbon monoxide.[4] The brain and heart are usually the most severely affected organs because they are the most sensitive to hypoxia.[5]

The rationale for the emergency treatment of carbon monoxide poisoning with hyperoxia is, first, to quickly increase tissue oxygenation by boosting blood oxygen content and, second, to shorten the time to restore blood oxygen-carrying capacity by accelerating carbon monoxide elimination. Cerebral oxygen delivery, however, is a function of both blood oxygen content and cerebral blood flow (CBF). CBF has long been known to decrease in response to hyperoxia in healthy research subjects.[6] One proposed mechanism linking hyperoxia to CBF is through oxygen's action as a respiratory stimulant[7,8] resulting in a decrease in Pa_{CO_2}. CBF is very sensitive to decreases in Pa_{CO_2}, decreasing approximately 2% for every mm Hg (0.133 kPa) decrease in Pa_{CO_2} below 40 mm Hg (5.3 kPa).[9,10] Any decrease in cerebral perfusion resulting from hypocapnia associated with hyperoxic treatment would offset the intended increase in oxygen delivery to the brain. The purpose of this study was to compare calculated cerebral oxygen delivery (D_{O_2}) in carbon monoxide–exposed research subjects treated with hyperoxia with and without measures to prevent hypocapnia.

MATERIALS AND METHODS

After receiving approval from the institutional Human Subjects Review Committee, signed informed consent was obtained from 9 male and 9 female research subjects between the ages of 18 and 47. All research subjects were nonsmokers, taking no medications, and within 20% of their ideal weight for their height. Before carrying out the protocol, all research subjects had venous blood hemoglobin concentration determined and underwent pulmonary function testing at the hospital's clinical laboratory. Female volunteers were studied in the first 2 weeks of their menstrual cycle to minimize the effects of progesterone on ventilation.[11]

Volunteers were tested in 2 sessions on separate days. Each involved a control period when baseline measurements were made, exposure of the research subjects to carbon monoxide, and then 1 of the 2 randomized "treatment" regimens. Treatment consisted of breathing oxygen-enriched gas with or without carbon dioxide added to maintain normocapnia. The order of the treatment was randomized by picking a marked piece of paper from a bag. The breathing circuits were balanced so that the research subjects were unable to discern the phase of the experiment or the type of treatment.

Research subjects were seated comfortably and had an indwelling catheter inserted into a forearm vein. They breathed through the circuit by means of a full facemask with a silicone seal (Hans-Rudolph, Inc., Kansas City, MO). Initial inspired gas was air while research subjects acclimated to the mask and circuit (10 to 20 minutes). After control measurements (10 minutes), research subjects were exposed to 1,000±200 ppm carbon monoxide in air until their carboxyhemoglobin (COHb) levels reached 10% to 12% (30 to 60 minutes). Venous blood samples were analyzed for COHb every 5 minutes. After exposure, research subjects were treated with either 100% oxygen (poikilocapnic hyperoxia) or with 96% to 100% oxygen in which the balance gas, carbon dioxide, was used to maintain normocapnia during increases in minute ventilation (normocapnic hyperoxia).

The circuit, which has been described previously,[12] includes a nonrebreathing valve, the inspiratory port of which is connected to an oxygen reservoir, and to which is directed a flow of oxygen (Figure 1). If minute ventilation exceeds the oxygen flow, additional gas, termed "reserve gas," is available from a compressed gas cylinder through a demand regulator. For poikilocapnic treatment, the reserve gas consisted of oxygen; for normocapnic treatment, the reserve gas consisted of

approximately 6% carbon dioxide balance oxygen. To the extent that minute ventilation exceeds resting levels, the reserve gas provides carbon dioxide to inspired gas in direct proportion to that increase. At a concentration of approximately 6% carbon dioxide, the net P_{CO_2} of inspired gas is such as to prevent changes in carbon dioxide elimination and thus end-tidal P_{CO_2}.[12] By adjusting the oxygen flow at rest to be slightly less than resting minute ventilation, research subjects inspired reservoir gas even at rest and thus were not alerted to an increase in ventilation by the opening of the demand regulator. Any increase in minute ventilation above resting levels increased the blood-to-alveolar partial pressure gradient for carbon monoxide but not carbon dioxide, thereby increasing the elimination of carbon monoxide while preventing hypocapnia.[12]

We measured mean middle cerebral artery blood velocity (MCAV) as an indicator of CBF.[13] A range-gated pulsed 2-MHz Doppler probe (Pioneer TCD, Nicolet Biomedical, Madison, WI) was positioned just

Figure 1.

Schematic of the circuit. Fresh gas is delivered by means of the fresh gas inlet and then fills the fresh gas reservoir. If the reservoir empties, the demand valve opens and the patient breathes the reserve gas (100% oxygen or 6% carbon dioxide, balance oxygen).

above the zygomatic arch, and the sample depth (45 to 50 mm) was adjusted until the trunk of the artery was insonated. The probe was then fixed in place with a harness for the rest of the experiment. Mean MCAV values were determined from a time average of the envelope of the Doppler frequency spectra.[14] Changes in mean MCAV were expressed as a percent of baseline values. Blood pressure and oxygen saturation were monitored noninvasively (AS/3, Datex-Ohmeda, Espoo, Finland). Because the end-tidal P_{CO_2} to P_{aCO_2} gradient was unlikely to change during the protocol, we measured end-tidal P_{CO_2} as an indicator of P_{aCO_2}. Gas was sampled from the face mask and analyzed for carbon dioxide (Capnomac Ultima, Datex-Ohmeda, Espoo, Finland) and carbon monoxide (Analytical Development Company, Hoddesdon, England). Expired flow was measured using a fast-response unidirectional flow transducer (SC520, VacuMed, Ventura, CA). Analog signals for P_{CO_2}, inspired carbon monoxide, and MCAV were digitized and recorded (Codas, Dataq Instruments, Inc., Akron, OH). Venous blood was drawn every 5 minutes and analyzed for percent COHb (OSM3, Radiometer, Copenhagen, Denmark). Half-time of elimination of COHb ($t_{1/2}$) was calculated by plotting percent COHb versus time and fitting an exponential curve of the form

$$COHb_t = COHb_0 \times e^{-kt}$$

to the plot. $t_{1/2}$ (in minutes) was obtained from the relation

$$t_{1/2} = \ln 2 / k.$$

Cerebral D_{O_2} is the product of CBF and blood oxygen content. MCAV values are not equivalent to absolute values of CBF, but changes in MCAV are directly proportional to changes in CBF.[13] We calculated a virtual cerebral D_{O_2} by multiplying mean MCAV by blood oxygen content (assuming all hemoglobin, except COHb, was fully saturated with oxygen). All values for a single patient were then expressed as fractional change from control.

Results were analyzed using a 2-way repeated measures analysis of variance (RM-ANOVA) in which the research subjects represented the repeated measures and time and treatment were each considered factors. To compare data with control values, a post hoc Dunnet's
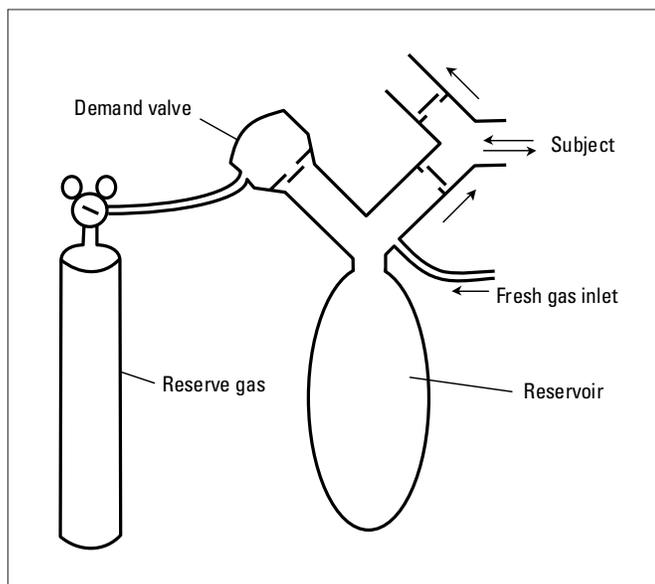
test was performed after a 1-way RM-ANOVA in which the research subjects represented the repeated measures and time was considered a factor. Results at 60 minutes of treatment and $t_{1/2}$ were compared using paired *t* tests. Results are reported as mean±SD along with boundaries of the 95% confidence interval (CI). A *P* value less than .05 was considered significant.

RESULTS

One male and 3 female research subjects were excluded because we could not obtain satisfactory MCAV signals during the initial control session. Anthropometric and pulmonary function data for the remaining research subjects are presented in the Table.

Poikilocapnic hyperoxic treatment increased minute ventilation and decreased end-tidal P_{CO_2} (*P*<.001, Figure 2), indicating that the respiratory response to hyperoxia remained intact in the presence of up to 12% COHb. In contrast, normocapnic hyperoxic treatment resulted in an even greater increase in minute ventilation (*P*<.001) without any change in P_{CO_2} (*P*=.4). This

increase in ventilation was associated with a 12±9 minutes (95% CI 7 to 17) or 21% decrease in $t_{1/2}$ of carbon monoxide elimination compared with poikilocapnic hyperoxia (45±8 versus 57±11 minutes; *P*<.05).

Exposure to carbon monoxide increased MCAV by 12.8±9.9% (95% CI 9.1 to 16.4; *P*<.01) above control. Once the hyperventilatory response to oxygen was established, MCAV decreased more during poikilocapnic hyperoxia than during isocapnic hyperoxia (*P*<.001; Figure 3). By the end of the study, MCAV was 9.4±13.6%

Figure 2.
Minute ventilation ($\dot{V}_E$) and end-tidal P_{CO_2} versus time during poikilocapnic (●) and normocapnic (○) hyperoxic "treatment." *Denotes significant difference from control (P<.05). †Denotes significant difference between treatments based on 2-way RM-ANOVAs.

Table.
Anthropometric data and control values for all research subjects included in the study.

Research Subject No. (Sex)	Age, y	Weight, kg	Height, cm	FRC, L	TLC, L	DLCO, mL/min/ mm Hg	[Hb], g/100 mL
1 (F)	47	60	163	2.4	5.0	21.4	12.6
3 (F)	23	57	161	2.3	4.8	21.4	13.7
4 (F)	24	64	163	2.9	5.5	24.8	12.0
5 (F)	38	48	157	2.8	5.1	23.2	10.5
7 (F)	20	54	169	3.0	5.9	24.9	12.9
9 (F)	19	59	154	1.8	4.4	24.1	12.2
10 (M)	22	87	179	3.8	7.7	32.6	13.5
11 (M)	20	60	176	3.2	6.3	30.3	13.6
12 (M)	20	67	171	2.9	6.2	34.6	14.0
13 (M)	20	68	172	2.7	6.5	36.9	14.7
14 (M)	23	64	173	3.9	7.1	31.3	14.6
15(M)	22	90	189	3.5	7.8	38.4	14.1
17 (M)	23	67	170	2.8	5.5	29.0	13.4
18 (M)	38	80	178	3.7	6.9	34.6	14.6
Mean±SD	26±7	66±12	170±9	3.0±0.6	6.1±1.1	29.1±5.8	13.3±1.2

FRC, Functional residual capacity; **TLC,** total lung capacity; **DLCO,** diffusivity of the lung for carbon monoxide; **[Hb],** hemoglobin concentration.

(95% CI −2.2 to −16.5; $P<.05$) lower during poikilocapnic hyperoxia compared with normocapnic hyperoxia. Cerebral DO_2, which is influenced by both CBF and COHb, was significantly greater ($9.7\pm13.3\%$; 95% CI 2.8 to 16.7; $P<.05$) during normocapnic hyperoxia than during poikilocapnic hyperoxia (Figure 3). We observed considerable intersubject variability in the effect of poikilocapnic hyperoxia on cerebral DO_2. Although some research subjects showed little decrease in cerebral DO_2 when exposed to hyperoxia, others showed a

Figure 3.

*MCAV and cerebral DO_2 versus time during poikilocapnic (●) and normocapnic (○) hyperoxic "treatment." **CO,** Carbon monoxide. *Denotes significant difference from control (P<.05). †Denotes significant difference between treatments based on 2-way RM-ANOVAs.*

marked decrease. In 3 research subjects, cerebral DO_2 decreased by more than 20% (research subjects 5, 12, and 13).

DISCUSSION

Our study shows that treating carbon monoxide–exposed research subjects with 100% oxygen decreased CBF, completely offsetting the effect of increased blood oxygen content on cerebral DO_2. Furthermore, maintaining normocapnia not only prevented the reduction in CBF and cerebral DO_2, but also accelerated the elimination of carbon monoxide. Our results are consistent with the observations of Kreck et al[15] who demonstrated that hyperoxic normocapnic "hyperventilation" improves whole body oxygen delivery and carbon monoxide elimination in mechanically ventilated carbon monoxide–poisoned sheep. However, they did not assess the independent effect of normocapnia nor did they specifically measure cerebral DO_2.

The stimulatory effect of oxygen on ventilation is not commonly appreciated today but has been described repeatedly in studies and texts beginning early in the past century.[7,8,16,17] Lambertsen et al[18] noted a decrease in CBF associated with hyperoxia and attributed it to the concomitant decrease in $PaCO_2$. Our work extends the observations about the relation between hyperoxia, hypocapnia, and reduced CBF by demonstrating that this mechanism is retained in the presence of 5% to 12% COHb.

Carbon dioxide was used in combination with oxygen for the treatment of carbon monoxide poisoning from the 1920s until after World War II.[19] The practice was introduced in 1922 by Henderson and Haggard[20] who reported dramatically faster recovery of severely carbon monoxide–poisoned patients treated with carbogen, a fixed concentration of carbon dioxide in oxygen. They attributed the improved effectiveness of carbogen over oxygen to ventilatory stimulation by carbon dioxide. Our study suggests that their patients may also have benefitted from a boost in cerebral DO_2. Treating patients with carbogen can, however, result in hypocap-

nia or hypercapnia, depending on the minute ventilation.[21] In contrast, the circuit used in our study maintains normocapnia independent of minute ventilation. Recently, Sasano et al[22] described an improvised version of our circuit consisting of a simple modification of a common self-inflating bag.
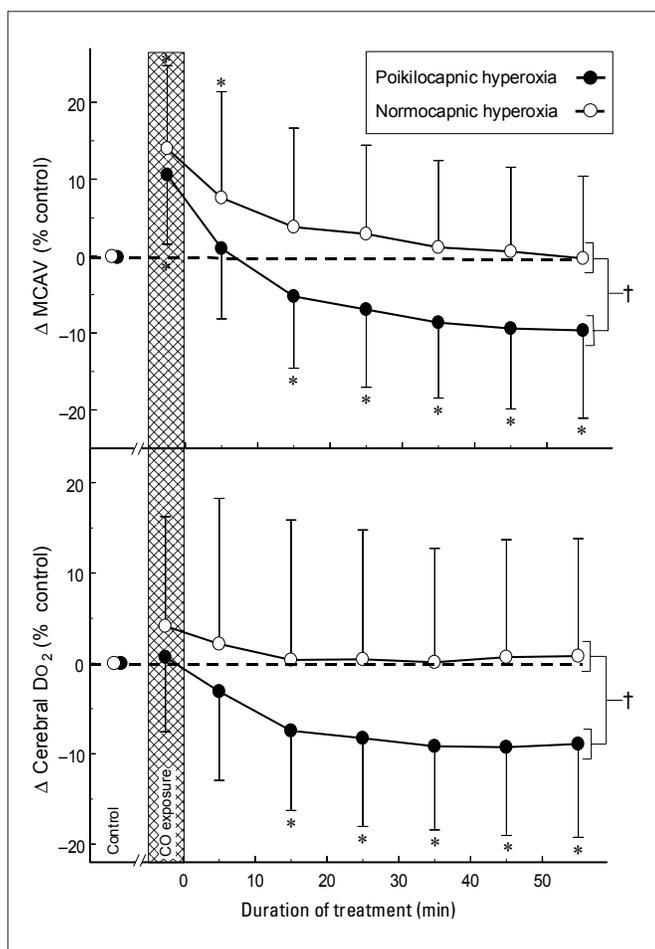
The presence of carbon monoxide in the blood diminishes oxygen carrying capacity, increasing the brain's dependency on perfusion for meeting its oxygen demands. In our study, by the end of exposure to carbon monoxide, a 10% decrease in oxygen carrying capacity (as a result of COHb) was offset by a 13% increase in CBF, resulting in no change in cerebral DO_2. During both treatments, oxygen content increased little, but with poikilocapnic hyperoxia, CBF decreased—markedly in some research subjects. In the research subject whose PCO_2 decreased the most, CBF and cerebral DO_2 decreased 33% and 26%, respectively, below control. This decrease in CBF is similar to that reported by Watson et al,[23] who observed up to a 31% reduction in CBF (measured by phase contrast magnetic resonance angiography) in research subjects not exposed to carbon monoxide breathing 100% oxygen. Even in patients without carbon monoxide poisoning, this degree of reduction in CBF can be associated with symptomatic brain ischemia,[24] raising the possibility that treatment with oxygen without maintaining normocapnia may contribute to symptoms and, possibly, adverse outcome.

Carbon monoxide poisoning also results in increased affinity of hemoglobin for oxygen,[25] impairing oxygen unloading to tissues. If patients become hypocapnic in response to hyperoxia, the oxyhemoglobin dissociation curve would be shifted even further to the left as a result of the Bohr effect.[25,26] In general, maintaining normocapnia should improve cerebral DO_2 by preventing a decrease in CBF, by minimizing the leftward shift of the oxyhemoglobin dissociation curve, and by accelerating carbon monoxide elimination.

There are a number of limitations to our study. First, because CBF could not be measured directly, we used MCAV as an index of CBF. The MCAV method assumes a constant diameter of the middle cerebral artery, a valid assumption for the range of PCO_2 experienced by our research subjects.[14] Little is known about the effect of carbon monoxide on the middle cerebral artery diameter in human beings, but one study has shown that carbon monoxide does not dilate large ex vivo rabbit cerebral vessels.[27] In any event, had carbon monoxide dilated the middle cerebral artery in our research subject, the resulting decrease in MCAV would have been interpreted as a paradoxical decrease in CBF; this was not the case.

A second limitation concerns the extrapolation of our results to patients. COHb levels in our research subjects were relatively low compared to those in carbon monoxide–poisoned patients. However, we expect that cerebrovascular reactivity to carbon dioxide would persist at higher levels of COHb and in the presence of cerebral hypoxia. Hypocapnia should readily abolish the mild direct vasodilatory effects of higher concentrations of carbon monoxide[28] as hypocapnia decreases CBF in the presence of high concentrations of such powerful cerebral vasodilators as halothane and isoflurane.[14,29,30] Furthermore, moderate hypocapnia ($PaCO_2$ of 27 mm Hg [3.6 kPa]) can overcome the cerebral vasodilatory effect of even severe hypoxemia (PaO_2 of 40 mm Hg [5.3 kPa]).[31]

A third limitation is that our study focused on the changes in cerebral DO_2 during oxygen treatment to the exclusion of other mechanisms by which carbon monoxide expresses its toxicity. These include nitric oxide–mediated tissue injury,[32] promotion of brain lipid peroxidation,[33] hastening apoptosis,[34,35] and interference with intracellular oxygen transport.[36] The effect on the degree of brain damage of increasing cerebral DO_2 after carbon monoxide exposure of unknown extent and duration is therefore difficult to predict for a given patient. However, because many of the direct toxic effects of carbon monoxide are dependent on, or exacerbated by, hypoxia,[37] it is reasonable to suggest that optimizing cerebral DO_2 early in the course of treatment should remain an important goal in the treatment of carbon monoxide poisoning.

The issue of maintaining normocapnia may have implications beyond increasing cerebral DO_2. For example, there may also be effects on regional distribu-

tion of blood flow in the brain, inhibition of intracellular oxygen transport and use, and effects on the extent of reperfusion injury. The net effect of maintaining normocapnia in severely poisoned patients is difficult to predict and will require further studies, particularly those focused on outcome.

In the absence of measures to maintain normocapnia, should carbon monoxide–poisoned patients be treated with oxygen? Although our results revealed a disturbing decrease in cerebral DO_2 on exposure of our carbon monoxide–exposed research subjects to oxygen, we did not address the extent of this effect in patients or the effect on tissue damage or outcome. These issues should be resolved before a change in practice is mandated.

In summary, we have demonstrated that treatment of mildly carbon monoxide–exposed research subjects with hyperoxia decreased cerebral blood flow and cerebral oxygen delivery. Maintaining normocapnia prevented the decrease in CBF and accelerated the elimination of carbon monoxide, resulting in improved cerebral oxygen delivery.

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