A Simple "New" Method to Accelerate Clearance of Carbon Monoxide

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The currently recommended prehospital treatment for carbon monoxide (CO) poisoning is administration of 100% O_2. We have shown in dogs that normocapnic hyperpnea with O_2 further accelerates CO elimination. The purpose of this study was to examine the relation between minute ventilation ($\dot{V}_E$) and the rate of elimination of CO in humans. Seven healthy male volunteers were exposed to CO (400 to 1,000 ppm) in air until their carboxyhemoglobin (COHb) levels reached 10 to 12%. They then breathed either 100% O_2 at resting $\dot{V}_E$ (4.3 to 9.0 L/min) for 60 min or O_2 containing 4.5 to 4.8% CO_2 (to maintain normocapnia) at two to six times resting $\dot{V}_E$ for 90 min. The half-time of the decrease in COHb fell from 78 ± 24 min (mean ± SD) during resting $\dot{V}_E$ with 100% O_2 to 31 ± 6 min ($p < 0.001$) during normocapnic hyperpnea with O_2. The relation between $\dot{V}_E$ and the half-time of COHb reduction approximated a rectangular hyperbola. Because both the method and circuit are simple, this approach may enhance the first-aid treatment of CO poisoning.

Carbon monoxide (CO) inhalation is the leading cause of fatal poisoning in the industrialized world (1). CO decreases the delivery of O_2 to the tissues by displacing O_2 from hemoglobin and forming carboxyhemoglobin (COHb). Primary treatment of CO poisoning consists of administration of 100% O_2 to increase dissolved O_2 in the plasma and displace CO from the O_2-binding sites on hemoglobin (Hb), thus restoring O_2 delivery to tissues. In cases of severe CO poisoning, the only additional therapy available is hyperbaric O_2. Unfortunately, hyperbaric chambers are unsuitable for emergency treatment, since they are relatively uncommon; for example, there are 340 hyperbaric chambers in the United States (2) and about 8 National Health Service facilities in the United Kingdom (3). Even in locations where hyperbaric chambers are available, delays in initiating therapy are inevitable because of the time needed to transport the patient, assemble trained personnel, and set up the chamber.

As early as 1922, CO_2-induced hyperpnea was shown to be effective in treating CO poisoning (4–6). Implementing the hyperpnea was problematic. Hyperpnea driven by fixed inspired concentrations of CO_2 of 5 to 10% was uncomfortable for conscious patients. Conversely, simple voluntary hyperventilation with 100% O_2 is inappropriate since it causes respiratory alkalosis, which in turn decreases cerebral blood flow and increases the affinity of Hb for O_2, both of which may aggravate brain hypoxia. This dilemma has been addressed by the recent development of a nonrebreathing circuit (7) that passively maintains normocapnia regardless of increases in minute ventilation ($\dot{V}_E$). Fisher and colleagues (1) established the feasibility of using the circuit to accelerate CO elimination in a dog model, in which increases in $\dot{V}_E$ to six times control values shortened the half-time of reduction of COHb ($t_{1/2}$) to less than half that at control $\dot{V}_E$.

Although the predicted relation between $\dot{V}_E$ and the rate of CO elimination during breathing of 20% O_2 is approximately that of a rectangular hyperbola (6), the actual relation, including that during breathing of 100% O_2, has not yet been determined. Therefore, the primary aim of the present study with humans was to examine the relation between $\dot{V}_E$ and the rate of COHb reduction during breathing of 100% O_2 and during normocapnic hyperoxic hyperpnea. We also wanted to determine whether hyperpnea could be sustained long enough to result in a clinically significant decrease in COHb.

METHODS

Subjects

After receiving approval from the Institutional Review Board of the University of Toronto and obtaining written informed consent, we studied seven healthy male volunteers from the hospital medical and scientific staff. All had normal pulmonary function, including CO diffusion capacity and Hb concentrations (Table 1). Only males were studied, in order to avoid the need for a larger cohort to account for an expected sex-related difference in the rate of CO elimination (8).

Principle of Technique

Our technique for maintaining normocapnia during hyperpnea is based on the following two principles, as described in detail by Sommer and colleagues (7): (*1*) the rate of CO_2 elimination is determined by the flow of "fresh gas" (not containing CO_2) to the alveoli; and (*2*) any $\dot{V}_E$ exceeding this flow of fresh gas will not affect Pa_{CO_2} if the additional inspired gas contains CO_2 at a partial pressure equal to that in the subject's mixed venous blood. Thus, hyperpnea with this technique does not increase the partial pressure gradient for CO_2 between pulmonary capillary blood and alveolar gas, but does increase the gradient for all other gases, including CO and O_2.

Our circuit (Figure 1) consisted of a face mask attached through a low-resistance heat and moisture exchanger to a large-bore nonrebreathing valve. The valve was connected to a 7-L water spirometer, which served as a fresh gas reservoir. During each phase of the experiment, inspired (fresh) gas was continually replenished at a fixed flow. An adjustable positive end-expiratory pressure (PEEP) valve, set at 2 cm H_2O and placed between the spirometer and the nonrebreathing valve, ensured that the inspired gas filled the spirometer during expiration. Resting (control) $\dot{V}_E$ was determined from a flowmeter adjusted so that the reservoir just emptied at the end of each inspiration, an indication that this flow of fresh gas exactly matched the subject's $\dot{V}_E$. The reserve gas consisted of 6% CO_2 in O_2, the net inspired CO_2 concentration depending on the $\dot{V}_E$.

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TABLE 1

SUBJECT ANTHROPOMETRIC DATA AND PULMONARY FUNCTION TESTS

Subject	Age (*yr*)	Height (*cm*)	Weight (*kg*)	Hb ($g \cdot 100\ ml^{-1}$)	$D_{L_{CO}}$ ($ml \cdot min^{-1} \cdot mm\ Hg^{-1}$)	TLC (*L*)	FRC (*L*)	VC (*L*)
1 □	50	181	77	15.8	32.7	8.5	4.6	6.2
2 +	39	176	62	15.1	28.4	7.0	4.9	3.9
3 ▽	44	178	71	14.3	28.0	6.4	3.4	4.7
4 ○	51	170	68	14.4	25.2	6.7	3.4	4.5
5 △	36	184	85	14.5	43.5	8.3	3.9	6.1
6 ×	48	179	74	14.7	33.9	8.4	4.6	5.1
7 ◇	32	175	70	15.1	34.3	6.4	3.2	5.0
Mean	43	178	72	14.8	32.3	7.4	4.0	5.1
SD	7	5	7	0.5	6.0	1.0	0.7	0.8

Protocol

Subjects were seated comfortably and breathed room air through the circuit for 5 to 10 min to allow them to accommodate to the face mask, and to allow measurement of their resting $\dot{V}_E$ with room air. Subjects were randomly assigned to one of the two "treatments" (described subsequently) and were then exposed to 400 to 1,000 ppm CO in air. Blood, sampled every 5 min from an indwelling 20-gauge intravenous cannula, was analyzed photometrically for COHb (OSM3; Radiometer A/S, Copenhagen, Denmark). After COHb reached 10 to 12%, subjects were either: (*1*) treated with 100% O_2 at resting $\dot{V}_E$ for 60 min (control); or (*2*) were subjected to normocapnic hyperoxic hyperpnea, during which time they were instructed to maintain a constant $\dot{V}_E$. A constant level of hyperpnea was sustained for the duration of each of these treatments as follows: Total flow into the spirometer was increased in a single step to a predetermined level equivalent to approximately two to six times the subject's resting $\dot{V}_E$. The P_{CO_2} of this gas was set to maintain end-tidal P_{CO_2} ($P_{ET_{CO_2}}$) within 3 mm Hg of its control value (normocapnia) for each subject at that level of $\dot{V}_E$ (7). Each subject was instructed to maintain the top of the spirometer bell within a narrow range at end-expiration; thus, his $\dot{V}_E$ matched the flow into the spirometer. Subjects were, however, free to adopt any pattern of breathing. After 60 min of treatment, subjects maintained hyperpnea for an additional 30 min to verify that the increased ventilatory level was sustainable. On a subsequent day, subjects returned and repeated the experiment with the other treatment. Two subjects volunteered for a third exposure to CO in order to evaluate the effect of an intermediate level of $\dot{V}_E$ (approximately twice control) on $t_{1/2}$. All expired CO was scavenged.

Data Collection

We monitored blood pressure and O_2 saturation noninvasively (AS/3; Datex, Helsinki, Finland). Gas was sampled from the face mask at a flow of 400 ml/min. The CO_2 concentration was measured with an infrared capnometer (Ametek Inc., Pittsburgh, PA) and corrected for P_{O_2}. Data were recorded with commercial electronic data acquisition software (WINDAQ/200; DATAQ Instruments, Inc., Akron OH).

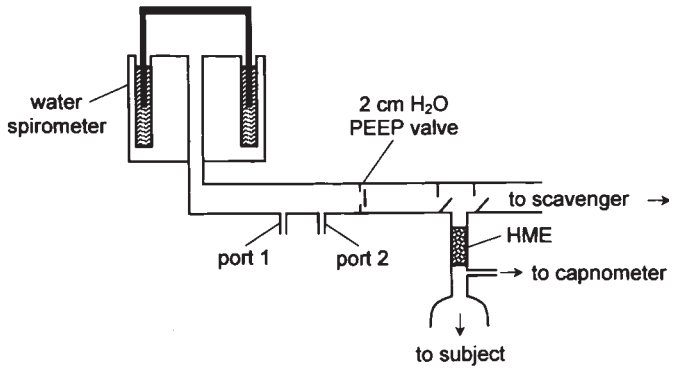

Figure 1. Schematic diagram of breathing circuit. Fresh gas was delivered via port 1 and inspired gas was sampled for CO analysis via port 2. The 2 cm H_2O PEEP valve prevented fresh gas from escaping into the expiratory limb of the circuit during expiration. HME = heat moisture exchanger.

Data Analysis

The time constant of COHb reduction (τ) during each treatment was determined from a curve fit by the method of least squares to values of log COHb plotted versus time. Data from the first 10 min of treatment were excluded from the calculation in order to avoid the effect of equilibration of CO between the various tissue compartments (1, 9). Values of $t_{1/2}$ were calculated as (ln 2)/τ. To facilitate pooling of the $t_{1/2}$ and $\dot{V}_E$ data from all subjects, we normalized the latter for estimated variations in body Hb content (6). Since the Hb concentration was relatively uniform in our subjects, $\dot{V}_E$ was divided by the subject's weight. Results were compared through paired *t* tests with Bonferroni's correction where appropriate; a value of $p < 0.05$ was considered significant. Data are expressed as mean ± SD.

RESULTS

There was no difference in COHb levels before the two treatments ($p = 0.39$). COHb decreased exponentially during both treatments (Figure 2). During resting $\dot{V}_E$ with 100% O_2 (7.1 ± 2.6 L/min), $t_{1/2}$ was 78 ± 24 min. Normocapnic hyperpnea decreased $t_{1/2}$, the decrease depending on the degree of hyperpnea (Figure 3). After 60 min, COHb levels decreased from 10.6 ± 0.4% to 6.2 ± 1.1% in subjects breathing 100% O_2, and from 11.0 ± 0.9% to 3.0 ± 1.0% during normocapnic hyper-

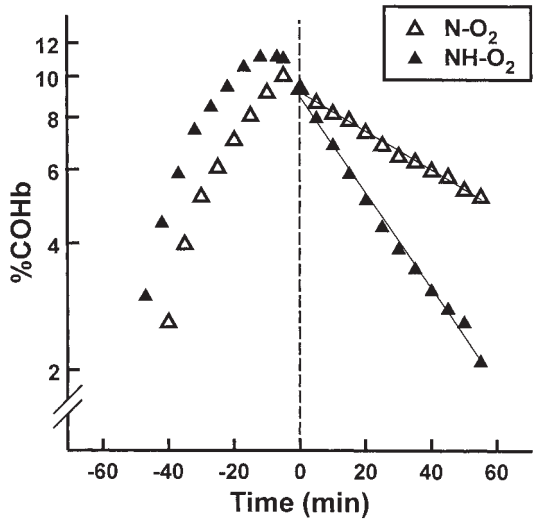

Figure 2. Percent COHb versus time for a representative subject (Δ in Figure 3) during exposure to CO and treatment with 100% O_2, normal ventilation (N-O_2, *open triangles*), and normocapnic hyperpnea (NH-O_2, *closed triangles*).

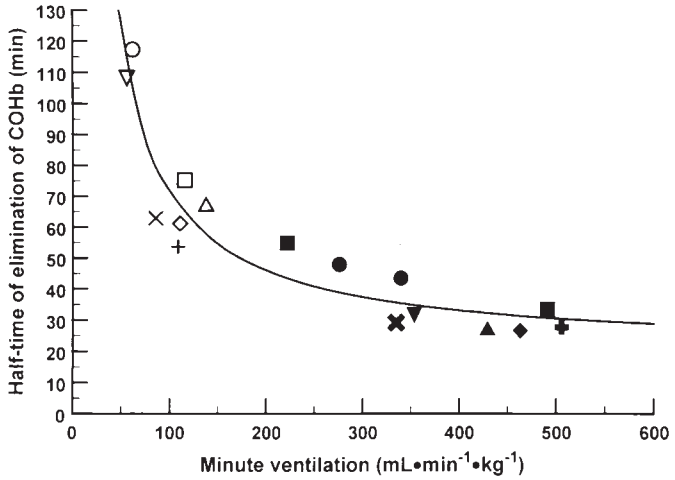

Figure 3. Half-time of COHb elimination versus $\dot{V}_E$ in all subjects (identified in Table 1). *Open symbols* represent values during resting ventilation, *closed symbols* represent values during normocapnic hyperpnea.

pnea; COHb levels after treatment with normocapnic hyperoxic hyperpnea were significantly less than those after treatment with 100% O_2 ($p < 0.0001$, paired *t* test). During hyperpnea, the $P_{ET_{CO_2}}$ and the rate × pressure product (an index of myocardial O_2 consumption [10]) did not differ from those obtained at rest (breathing air or room air plus CO). All subjects maintained hyperpnea for 90 min without difficulty. As compared with ventilation with room air (without and with CO), subjects breathing 100% O_2 spontaneously (without control of $P_{ET_{CO_2}}$) had a greater $\dot{V}_E$ (7.1 ± 2.6 L/min versus 5.6 ± 1.5 L/min, $p < 0.05$) and lower $P_{ET_{CO_2}}$ (39.4 ± 3.1 mm Hg versus 42.2 ± 2.1 mm Hg, $p < 0.05$). None of the subjects was aware of his increased $\dot{V}_E$.

DISCUSSION

In our subjects, moderate normocapnic hyperoxic, hyperpnea accelerated the clearance of CO as compared with that during control $\dot{V}_E$ with 100% O_2. The $t_{1/2}$ decreased in a hyperbolic fashion as $\dot{V}_E$ increased. Our subjects were able to sustain a $\dot{V}_E$ up to six times greater than their resting levels with room air for at least 90 min, a time sufficient to reduce initial levels of COHb by about 85%.

Investigators had earlier noted that both dogs and human patients respond to severe poisoning with coal gas (containing about 30% CO) with hyperventilation followed by hypoventilation (4) (*see also* Figure 10 in Norman and Ledingham [11]). This hypoventilation was the limiting factor in treating CO-poisoned patients with 100% O_2, the only known remedy at the time. Carbogen (95% O_2, 5% CO_2) was introduced in 1922 by Henderson and Haggard (12) for overcoming the secondary hypoventilation characteristic of CO poisoning. However, its use declined and it was eventually abandoned for this purpose as a result of the following three developments. The first was the introduction, after World War II, of a practical means of mechanical ventilation. The second was the submission of a report to the Medical Research Council (UK) (13) citing such complications as exacerbation of metabolic acidosis and post-exposure shock. In its stead, the authors recommended the use of pure O_2 and, if necessary, mechanical ventilation in patients in respiratory failure. And third, in 1960, Smith and Sharp (14) reported the first successful treatment of CO-poisoned patients with hyperbaric O_2. This became the preferred treatment for severe CO poisoning (2, 15, 16), resulting in the complete abandonment of carbogen for this purpose since about 1970.

Discontinuing the use of carbogen to treat hypoventilation may have been reasonable, but we suggest that abandoning hyperpnea for the treatment of CO poisoning was premature. One could reason that hyperpnea without CO_2 added to the inspirate is not a viable treatment option, since it risks hypocapnia, which increases the affinity of Hb for O_2 and significantly decreases cerebral blood flow (17), both of which decrease O_2 delivery to the brain. On the other hand, using carbogen as the inspired gas prevents hypocapnia, but risks hypercapnia and respiratory distress and, as discussed earlier, has been associated with a number of other undesirable effects. In contrast, the circuit of Sommer and colleagues (7) simultaneously and passively minimizes any change in Pa_{CO_2} regardless of $\dot{V}_E$, and accelerates CO elimination by widening the blood–alveolar gradient for CO.

Therapeutic Implications

Several factors should be considered in evaluating the potential of normocapnic hyperoxic hyperpnea for the first-aid treatment of CO poisoning. First, would it be effective in patients with very high levels of COHb? For ethical reasons, we limited COHb levels in our subjects to 10 to 12%, or about the same levels as found in heavy smokers, but much less than would result from severe CO poisoning. Nevertheless, our approach should be equally effective at higher COHb levels, because the distribution of CO between blood and tissues is approximately constant over the range of 0 to 60% COHb (18), and because the same principles governing CO elimination apply. Indeed, at higher COHb levels, normocapnic hyperpnea should actually be more effective in terms of the absolute volume of CO eliminated per unit time. As compared with breathing 100% O_2 at resting $\dot{V}_E$, normocapnic hyperpnea approximately tripled the rate of reduction of COHb (Figure 3), thus providing about the same benefit as that obtained with hyperbaric O_2 therapy (1, 8).

Second, can normocapnic hyperoxic hyperpnea be used in patients unwilling or unable to generate the required increases in $\dot{V}_E$? The results shown in Figure 3 suggest that even a modest increase in $\dot{V}_E$ will produce a marked decrease in $t_{1/2}$, particularly in patients with an initially low $\dot{V}_E$. Thus, a $\dot{V}_E$ as low as 200 ml/min/kg (14 L/min in a 70 kg patient) should provide most of the benefit available from hyperpnea. Our subjects were able to sustain up to three times this $\dot{V}_E$ for 90 min, a time sufficient to decrease COHb by 85%. In unconscious patients requiring manual ventilation, normocapnia can be maintained while increasing $\dot{V}_E$ by attaching the reserve gas limb of the circuit of Sommer and colleagues (7) to the intake manifold of the self-inflating bag.

Even if no voluntary hyperpnea is planned, it may be prudent to maintain normocapnia when providing 100% O_2 to all patients with CO poisoning. In our study, subjects breathing 100% O_2 had a decrease in their $P_{ET_{CO_2}}$ of 2.9 mm Hg (range: 0 to 5.0 mm Hg) as compared with that when breathing air. If cerebrovascular reactivity to CO_2 is retained during CO poisoning, cerebral blood flow and O_2 delivery could fall by an average of 7% (17). By preventing hypocapnia, not only would cerebral blood flow be maintained (19), but there would be an even greater involuntary increase in $\dot{V}_E$ (20), which would help eliminate CO. Furthermore, there would be no risk to patients as a result of maintaining normocapnia.

Third, would early treatment affect the prognosis in CO poisoning? Assuming that the mechanism of toxicity of CO includes a direct intracellular effect (21, 22) in addition to that due to hypoxemia, three factors—duration of exposure to CO ("soaking period"), COHb levels, and duration of tissue hyp-

oxia—will determine the extent of tissue injury. The delay in equilibration of CO between blood and tissues (9), and between the blood of the mother and fetus during pregnancy (23), implies that during exposure to lethal levels of CO there is always a gradient between blood and tissue P_{CO}. Indeed, this gradient favoring continued entry of CO into tissues (9) and fetal blood (23) persists for at least 30 min after initiation of treatment with 100% O_2, and for even longer with air (9). Early maximally effective treatment would not only lower COHb and relieve hypoxia sooner, but provide the additional benefit of minimizing the peak tissue and fetal CO load (23).

Conclusions

Normocapnic hyperoxic hyperpnea increased the rate of elimination of CO in human subjects by two to three times that with normal breathing of 100% O_2, the current prehospital treatment for CO poisoning. With appropriate preparation, this technique can be applied at the time of rescue with a portable circuit. Provision of more rapid CO elimination earlier in the course of treatment for CO poisoning may improve the prognosis for this, the most common cause of poisoning.

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