Isocapnic Hyperventilation Increases Carbon Monoxide Elimination and Oxygen Delivery

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Hyperventilation with mixtures of O_2 and CO_2 has long been known to enhance carbon monoxide (CO) elimination at low HbCO levels in animals and humans. The effect of this therapy on oxygen delivery (D_{O_2}) has not been studied. Isocapnic hyperventilation utilizing mechanical ventilation may decrease cardiac output and therefore decrease D_{O_2} while increasing CO elimination. We studied the effects of isocapnic hyperventilation on five adult mechanically ventilated sheep exposed to multiple episodes of severe CO poisoning. Five ventilatory patterns were studied: baseline minute ventilation ($RR \cdot V_T$), twice ($2 \cdot RR$) and four times ($4 \cdot RR$) baseline respiratory rate, and twice ($2 \cdot V_T$) and four times ($4 \cdot V_T$) baseline tidal volume. The mean carboxyhemoglobin (HbCO) washout half-time ($t_{1/2}$) was 14.3 ± 1.6 min for $RR \cdot V_T$, decreasing to 9.5 ± 0.9 min for $2 \cdot RR$, 8.0 ± 0.5 min for $2 \cdot V_T$, 6.2 ± 0.5 min for $4 \cdot RR$, and 5.2 ± 0.5 min for $4 \cdot V_T$. D_{O_2} was increased during hyperventilation compared with baseline ventilation for $2 \cdot V_T$, $4 \cdot RR$, and $4 \cdot V_T$ ventilatory patterns. Isocapnic hyperventilation, in our animal model, did not alter arterial or pulmonary blood pressures, arterial pH, or cardiac output. Isocapnic hyperventilation is a promising therapy for CO poisoning.

Isocapnic hyperventilation has been proposed as a possible "new" therapy for carbon monoxide (CO) poisoning (1). Early studies of hyperventilation for CO poisoning used unassisted ventilation with a fixed fraction of carbon dioxide (CO_2) in oxygen (O_2) (2–4), whereas Fisher and coworkers more recently used a passive apparatus that introduced CO_2 at rates proportional to minute ventilation ($\dot{V}_E$) (5). The benefit of unassisted isocapnic hyperventilation, as practiced before the onset of mechanical ventilation, was limited because increased CO elimination rates depend on spontaneous or voluntary increases in $\dot{V}_E$. Takeuchi and coworkers have proven that 90 min of spontaneous hyperventilation, 2 to 6 times baseline $\dot{V}_E$, is possible in conscious volunteers with low levels of carboxyhemoglobin (HbCO) (6), but these subjects may not adequately model the typical CO-poisoned patient. As predicted by mathematical models (7–10) and confirmed in dogs (1) and humans (6), large increases in $\dot{V}_E$ are required to significantly increase rates of CO elimination. An optimal level of hyperventilation may not be spontaneously sustainable in clinical practice because the time required to decrease HbCO levels to 25% of their initial value is up to 160 min for normobaric O_2 (NBO) at baseline $\dot{V}_E$ (11).

Hyperventilation therapy using mechanical ventilatory support is a viable option but cardiac output may be compromised by increased intrathoracic pressure and reduced venous blood return to the heart. If this were the case, O_2 delivery to tissue (D_{O_2}) would decline acutely during therapy when tissue P_{O_2} is at low levels, potentially worsening the clinical condition of the patients. Fisher and coworkers demonstrated a dramatic increase in CO elimination in dogs mechanically ventilated with a tidal volume ($\dot{V}_T$) of 50 ml $\cdot$ kg^{-1} when isocapnic hyperventilation was compared with normal ventilation with NBO or room air (RA) ventilation. Because the order of each treatment was fixed and each therapy arm was performed at different mean HbCO levels (51% for RA, 25% for NBO, and 6% for hyperventilation), this study was not able to address the issue of D_{O_2} during hyperventilation at high HbCO levels.

We used an animal model of multiple severe CO poisonings to assess the effect of isocapnic hyperventilation on CO elimination and D_{O_2} at high HbCO levels. Because large increases in $\dot{V}_T$ may result in increased alveolar ventilation ($\dot{V}_A$) but decreased cardiac output compared with increases in respiratory rate (RR), we also examined the effect of respiratory pattern on CO elimination and D_{O_2}.

METHODS

Animal Model

This study was approved by the University of Washington (Seattle, WA) Institutional Animal Care and Use Committee and the National Institutes of Health guidelines for animal use and care were followed throughout. Five adult sheep (27.5–36 kg) of either sex were studied. The animals were premedicated by intramuscular injection of xylazine (1.0 mg $\cdot$ kg^{-1}), anesthetized by intravenous administration of thiopental sodium (20 mg $\cdot$ kg^{-1}), and intubated. Anesthesia was maintained throughout the study, using a constant intravenous infusion of thiopental sodium, titrated to suppress hemodynamic and motor responses to noxious stimuli. The animals were initially ventilated with a piston animal ventilator (Harvard Apparatus, Hollison, MA) with a V_T from 10 to 15 ml $\cdot$ kg^{-1}, zero positive end-expiratory pressure (PEEP), and a respiratory rate (RR) set to maintain the arterial P_{CO_2} between 35 and 40 mm Hg. A Swan-Ganz pulmonary artery catheter was placed via the right external jugular vein and arterial and venous catheters were placed in the left groin. The animal was then placed in the prone posture for the remainder of the study. Animals were killed after completion of the study, using a concentrated pentobarbital injection. Data collected include hemoglobin (Hb) concentration, heart rate (HR), arterial pressure (Pa), pulmonary arterial pressure (Ppa), pulmonary capillary wedge pressure (Pcw), thermodilution cardiac output, airway pressures, inspired and exhaled CO_2 concentrations, arterial and mixed venous blood gases (pH, P_{O_2}, P_{CO_2}), and arterial HbCO levels. All exhaust gas from the ventilators was scavenged and released outside the building with ambient air tested continuously for CO.

Treatment Trials

Each animal was exposed to six cycles of CO poisoning and treatment. Poisoning was accomplished by inhalation of 0.6% CO gas in air for 20 to 30 min, delivered via ventilator, until arterial [HbCO] reached 65 to 75%. Ventilation treatment trials were performed with a Servo 900C ventilator (Seimens-Elema, Solna, Sweden) at varying V_T, RR, and $F_{I_{CO_2}}$ (fraction of inspired carbon dioxide; balance O_2). After the first poisoning, the animals were ventilated with the Servo ventilator at the baseline ventilatory pattern ($RR \cdot V_T$) with an RR of 10 breaths $\cdot$ min^{-1} and a V_T adjusted to maintain P_{CO_2} between 35 and 40 mm Hg. The initial HbCO measurement and D_{O_2} calculation for each trial were made immediately after switchover to $CO_2:O_2$ ventilation and continued every 5 min until [HbCO] fell below 20%, at which time poisoning was reinstituted. The remaining five trials, performed in varied order, were used to test different ventilatory treatments and

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TABLE 1

DESCRIPTION OF THE FIVE TREATMENTS
FOR CO POISONING STUDIES

Trial	Respiratory Rate	Tidal Volume	$\dot{V}_E$	$\dot{V}_A$
RR · V$_T$	Baseline	Baseline	Baseline	Baseline
2 · RR	2 · Baseline	Baseline	2 · Baseline	2 · Baseline
2 · V$_T$	Baseline	2 · Baseline	2 · Baseline	2.5 · Baseline
4 · RR	4 · Baseline	Baseline	4 · Baseline	4 · Baseline
4 · V$_T$	Baseline	4 · Baseline	4 · Baseline	5.6 · Baseline

Definition of abbreviations: RR · V$_T$ = baseline trial; RR = baseline respiratory rate; V$_T$ = baseline tidal volume; $\dot{V}_E$ = minute ventilation; $\dot{V}_A$ = alveolar ventilation (estimated).
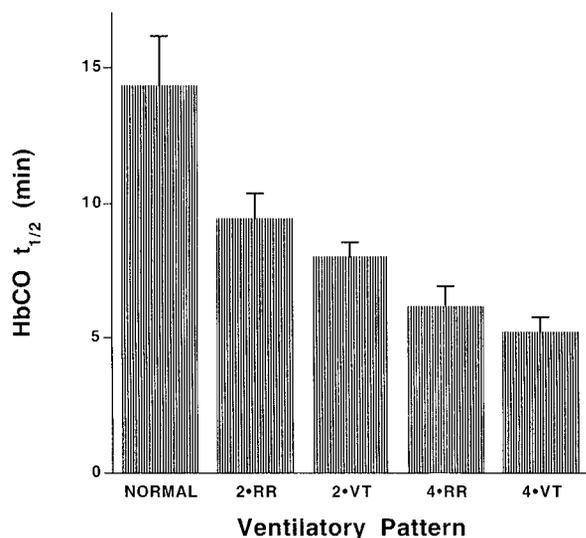
are listed in Table 1. For all hyperventilation trials, the amount of inspired CO_2 was adjusted to maintain arterial P_{CO_2} between 30 and 40 mm Hg.
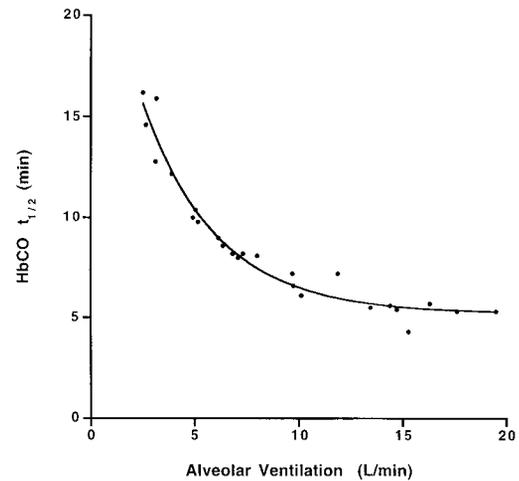
Data Analysis

CO elimination rates were compared across treatment trials in each animal, allowing each sheep to serve as its own control, increasing the power of the study and limiting the number of animals required. The HbCO washout half-time ($t_{1/2}$) of each of the therapies was determined graphically for each animal studied by plotting HbCO levels over time for each treatment trial. Do_2 (ml $O_2 \cdot min^{-1} \cdot kg^{-1}$) is the product of blood O_2 content and the cardiac index (CI). O_2 saturation (%) = 100% − HbCO (%), because FI_{O_2} remained above 550 mm Hg throughout treatment and all heme units were saturated with O_2 or CO. All comparisons used analysis of variance (ANOVA), with $p < 0.05$ indicating significance. Because larger values of HbCO and Do_2 show more variability than smaller values, statistical tests that assume constant variance will not yield accurate p values. Log(HbCO) and log(Do_2) showed similar variability across their ranges of values; therefore, statistical tests were performed with the logarithms of these variables. To avoid multiple comparison effects, the Fisher protected least significant difference was used. The first trial for all animals, always performed at normal ventilation, functioned only to "load" extravascular tissues with CO and was not included in any of the analyses.

RESULTS

Increases in $\dot{V}_E$ are associated with decreasing HbCO $t_{1/2}$ (Figure 1). In the five sheep studied, the mean HbCO $t_{1/2}$ was 14.3 ±

Figure 2. HbCO $t_{1/2}$ versus alveolar ventilation ($\dot{V}_A$). $\dot{V}_A$ is calculated using measured $\dot{V}_E$ and an estimated fixed deadspace fraction equal to 35% of baseline V$_T$. HbCO half-lives for trials RR · V$_T$, 2 · RR, 2 · V$_T$, 4 · RR, and 4 · V$_T$ for all sheep are plotted. The fitted curve is represented by HbCO $t_{1/2} = \alpha + \beta \exp(\gamma \dot{V}_A)$, where $\alpha = 5.20$ (± 0.33), $\beta = 21.2$ (± 1.84), and $\gamma = -0.279$ (± 0.031). *See* Table 1 for a description of ventilatory patterns.

1.6 min for baseline ventilation (RR · V$_T$), 9.5 ± 0.9 min when RR was doubled (2 · RR), 8.0 ± 0.5 min when V$_T$ was doubled (2 · V$_T$), 6.2 ± 0.5 min when RR was quadrupled (4 · RR), and 5.2 ± 0.5 min when V$_T$ was quadrupled (4 · V$_T$). The HbCO half-lives for each ventilatory pattern are significantly different from the HbCO half-lives for all other ventilatory patterns ($p < 0.05$).

$\dot{V}_A$ can be estimated for each level of $\dot{V}_E$ by assuming a fixed deadspace (Vds) equal to 35% of baseline V$_T$ (unpublished data for normal prone sheep). Figure 2 demonstrates the relationship between HbCO $t_{1/2}$ and $\dot{V}_A$, described by an exponential function: HbCO $t_{1/2} = \alpha + \beta \exp(\gamma \dot{V}_A)$, where: $\alpha = 5.20$ (± 0.33), $\beta = 21.2$ (± 1.84), and $\gamma = -0.279$ (± 0.031). This exponential function fit the data better ($r^2 = 0.961$) than an
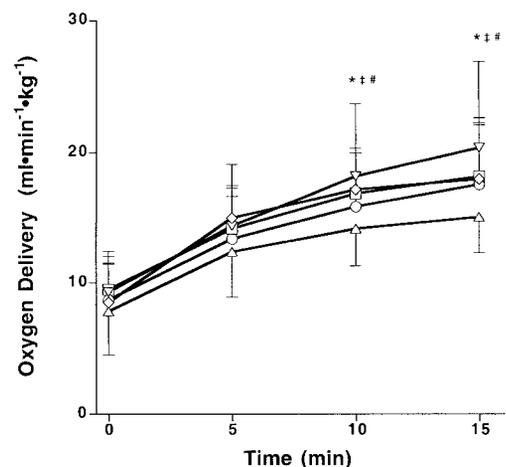
Figure 1. Mean HbCO $t_{1/2}$ for various ventilatory patterns. The HbCO $t_{1/2}$ for each ventilatory pattern is significantly different from the $t_{1/2}$ of all other ventilatory patterns ($p < 0.05$). *Vertical bars* indicate 1 standard deviation (SD). *See* Table 1 for description of ventilatory patterns.

Figure 3. Oxygen delivery during treatment with various levels of isocapnic ventilation. Differences are noted when $p < 0.05$: *RR · V$_T$ significantly different from 4 · V$_T$, ‡RR · V$_T$ significantly different from 4 · RR, #RR · V$_T$ significantly different from 2 · V$_T$. *Open triangles*, RR · V$_T$; *open circles*, 2 · RR; *open squares*, 2 · V$_T$; *open diamonds*, 4 · RR; *open inverted triangles*, 4 · V$_T$. *Vertical bars* indicate 1 standard deviation (SD). *See* Table 1 for a description of ventilatory patterns.

TABLE 2
HEMODYNAMIC AND GAS EXCHANGE PARAMETERS DURING FIVE
TREATMENT TRIALS USING DIFFERENT VENTILATORY PATTERNS*

Parameter	RR · V_T	2 · RR	2 · V_T	4 · RR	4 · V_T
Pa (mean), mm Hg	86 ± 20	93 ± 10	85 ± 13	87 ± 6	93 ± 14
Ppa (mean), mm Hg	18 ± 4	17 ± 5	19 ± 2	18 ± 5	18 ± 2
Pcw, mm Hg	10 ± 3	9 ± 2	11 ± 2	10 ± 1	10 ± 2
HR, min^{-1}	111 ± 7	118 ± 10	119 ± 13	125 ± 18[†]	116 ± 13
CI, ml · min^{-1} · kg^{-1}	146 ± 30	151 ± 40	154 ± 25	153 ± 31	137 ± 27
pH (arterial)	7.40 ± 0.05	7.43 ± 0.04	7.40 ± 0.03	7.40 ± 0.02	7.44 ± 0.03
Pa_{O_2}, mm Hg	588 ± 21	606 ± 35	603 ± 40	576 ± 61[‡,§]	615 ± 29[†,‖]
Pa_{CO_2}, mm Hg	37.3 ± 2.7	35.5 ± 2.6	33.9 ± 1.9[†]	34.2 ± 2.7[†]	32.3 ± 2.7[†,‡]

Definition of abbreviations: CI = cardiac index; HR = heart rate; RR · V_T = baseline trial; Pa = systemic arterial blood pressure; Pa_{CO_2} = arterial pressure of carbon dioxide; Pa_{O_2} = arterial pressure of oxygen; RR = baseline respiratory rate; Vt = baseline tidal volume; Ppa = pulmonary arterial pressure; Pcw = pulmonary capillary wedge pressure.

* mean values ± interanimal SD.
[†] $p < 0.05$ compared with RR · V_T.
[‡] $p < 0.05$ compared with 2 · RR.
[§] $p < 0.05$ compared with 2 · V_T.
[‖] $p < 0.05$ compared with 4 · RR.

exponential function with an asymptote at zero ($r^2 = 0.860$) or a quadratic polynomial ($r^2 = 0.925$).

Do_2 was increased during treatment with all patterns of hyperventilation compared with baseline ventilation (Figure 3). The difference in Do_2 reached significance for 2 · V_T, 4 · RR, and 4 · V_T groups compared with RR · V_T at 10 and 15 min.

Hemodynamic and gas exchange parameters for all five patterns of ventilation averaged over the duration of each treatment period in all five animals are listed in Table 2. Mean Pa, mean Ppa, Pcw, CI, and arterial pH were not different ($p > 0.05$) across all ventilation patterns. Arterial Pco_2 was less for the 2 · V_T, 4 · RR, and 4 · V_T groups than for the RR · V_T group ($p < 0.05$). The few differences in HR and arterial Po_2 between ventilatory patterns that reached significance are noted in Table 2.

DISCUSSION

Our study adds to the findings of Fisher and colleagues and Takeuchi and colleagues, that isocapnic hyperventilation increases the rate of CO elimination. Our study differs from previous work in four areas. (*1*) We used a multiple poisoning model, with each animal subject exposed to all treatment permutations in varied order, greatly enhancing the statistical power of the study. The multiple poisoning model developed in our laboratory has been shown to be hemodynamically stable and yields highly reproducible HbCO $t_{1/2}$ for up to seven repeat poisonings (12, 13); (*2*) we studied the effects of isocapnic hyperventilation at clinically relevant HbCO levels. Takeuchi and coworkers used low HbCO levels in human volunteers, with a peak [HbCO] of 12%. Fisher and coworkers studied dogs with severe CO poisoning, but each treatment was performed at different HbCO levels, the order of the treatments was not varied, and isocapnic hyperventilation was performed on each animal at the lowest HbCO levels (mean [HbCO] approximately 11%). While HbCO $t_{1/2}$ is relatively independent of HbCO levels, other clinically relevant variables may depend heavily on HbCO levels. For example, Do_2 measurements are highly related to HbCO levels. Do_2 will be higher when HbCO is lower, particularly under high $F_{I_{O_2}}$ conditions, because heme sites not occupied by CO would be occupied by O_2. In addition, tissue oxygen debt and acidosis, CO_2 production, myocardial contractility, and the rate of venous blood return may also vary significantly with HbCO levels; (*3*) we measured Do_2 during all treatment trials, whereas previous

studies had not; and (*4*) we studied the effects of RR and V_T increases on HbCO $t_{1/2}$ and Do_2 by varying RR and V_T independently over a 4-fold range.

Isocapnic hyperventilation increased CO elimination in a dose-dependent manner, with a 4-fold increase in V_T resulting in a 2.75-fold increase in the CO elimination rate (Figure 1). This finding is consistent with the findings of increased CO elimination with isocapnic hyperventilation by Fisher and colleagues in dogs (2.33-fold) and by Takeuchi and colleagues in human volunteers (2.52-fold), using comparable levels of hyperventilation. A similar relationship between hyperventilation and CO elimination is predicted by the CFK model of CO kinetics described by Coburn, Forster, and Kane (7).

Ventilatory pattern affects CO elimination. A higher V_T and lower RR results in faster CO elimination than a higher RR and lower V_T at the same overall $\dot{V}_E$ (Figure 1). Presumably, high V_T ventilation results in a lower deadspace fraction (Vds/V_T) and higher $\dot{V}_A$ than low V_T ventilation. The relationship between HbCO $t_{1/2}$ and $\dot{V}_A$ (estimated) suggests an upper limit of effective ventilation because HbCO $t_{1/2}$ does not change significantly when $\dot{V}_A$ is increased from 15 to 20 L/min (Figure 2). The relationship between CO elimination and $\dot{V}_A$ in our study, diminishing effect at higher $\dot{V}_A$, is consistent with the CFK mathematical model, the findings of Takeuchi and coworkers in humans, and a diffusion limitation to CO transport in the lung.

Do_2 is likely to be at least as relevant an end point as HbCO $t_{1/2}$ because a therapy that results in a decreased Do_2 while increasing CO elimination could possibly result in greater morbidity than more conservative treatment. We observed a dose-dependent increase in Do_2 during isocapnic hyperventilation in our prone sheep model; for increases in $\dot{V}_E$ we demonstrate increases in Do_2 (Figure 3). Cardiac index was not attenuated by any of the patterns of hyperventilation in this study, even with V_T as high as 60 ml · kg^{-1} (Table 2). HbCO levels fell faster during the hyperventilation trials, resulting in increased Do_2 compared with control.

Isocapnic hyperventilation did not cause overt changes in hemodynamics, gas exchange, or lung mechanics. Mean Pa did not decrease with hyperventilation. Likewise, Ppa and Pcw were not altered. Arterial Po_2 increased during three of the four hyperventilation patterns even under conditions of "high stretch ventilation" ($V_T = 60$ ml · kg^{-1}) and baseline Po_2 values were unchanged between trials, even after multiple exposures to high V_T ventilation. Airway pressures and arterial Pco_2 re-

turned to normal after each treatment trial. It should be noted that the lack of significant hemodynamic or pulmonary alterations during hyperventilation is demonstrated in prone sheep; the hemodynamic effects of positive-pressure hyperventilation in CO-poisoned supine humans remain unknown. The size of V_T in this and a previous animal study (dog) of isocapnic hyperventilation for CO poisoning is far greater than what is currently recommended for patients with acute respiratory distress syndrome (ARDS) (14). However, we are not aware of any studies that demonstrate lung damage from large $\dot{V}_E$ or V_T ventilation in normal lungs. In fact, an abstract demonstrated no lung damage in burn patients ventilated at 2- to 10-fold baseline $\dot{V}_E$ (15). In addition, sustained spontaneous isocapnic hyperventilation in normal human volunteers was well tolerated (6). Future studies of human victims of CO poisoning will be needed to address the effect of mechanically induced hyperventilation on lung function.

Although the $2 \cdot V_T$, $4 \cdot RR$, and $4 \cdot V_T$ trials had significantly lower mean arterial P_{CO_2} than the baseline ventilation trial, the P_{CO_2} was not significantly different between any of the hyperventilation trials. The difference in P_{CO_2} between the highest and lowest $\dot{V}_E$ was only 5 mm Hg and not clinically significant. In this study, $F_{I_{CO_2}}$ was adjusted manually for each of the five levels of ventilation. It is possible that a device such as the one used by Fisher and coworkers could have been used to keep P_{CO_2} within a tighter range.

We used a sheep model of severe CO poisoning for several reasons. First, sheep have been used by multiple investigators in the past to study physiologic effects of CO and CO elimination under a variety of conditions, and the kinetics of CO association/dissociation from sheep Hb have been well studied (16–21). Second, because sheep Hb has a lower affinity (M) for CO (140–150) than most other species ($\sim$ 250) they lend themselves more readily to the study of multiple repeat poisoning (21); a similar study in dogs would have required nearly 24 h. Finally, previous studies in our laboratory have observed stable hemodynamic variables and gas exchange parameters in sheep with multiple poisonings (12, 13), findings confirmed in this study. Because the treatment effect of hyperventilation is normalized to tidal breathing of pure O_2 in each animal we believe the fractional improvement in CO elimination rates would apply across species. This appears to be the case because previous studies of hyperventilation in dogs and humans report similar results (1, 6).

Hyperventilation with exogenous CO_2 and O_2 may result in hypocapnia or hypercapnia if $\dot{V}_E$ and $F_{I_{CO_2}}$ are not well matched. Hypocapnia is a potentially dangerous complication resulting in lower tissue P_{O_2} due to further increase in the affinity of Hb for O_2 (in addition to the increased affinity caused by CO) as well as cerebral vasoconstriction (22). Hypercapnia, on the other hand, is associated with mild increases in cardiac output and systolic Pa in critically ill patients (23), increases in D_{O_2} in animals (24), and a right shift in the oxyhemoglobin dissociation curve, which would counter the CO-induced increase in Hb–O_2 affinity. Hyperventilation with excessive levels of CO_2 may be safer than hyperventilation without adequate levels of exogenous CO_2. Considering the risks of hypocapnia and the decreasing effect of hyperventilation for CO removal at very high $\dot{V}_E$, it may be advisable in clinical practice to use a fixed $F_{I_{CO_2}}$ gas source such as Carbogen (5% CO_2 + 95% O_2) and an initial recommended $\dot{V}_E$ (perhaps 20 L/min). If isocapnic hyperventilation for CO poisoning is attempted in humans, whether a fixed or variable source of CO_2 is used, care must be taken to ensure that eucapnea is maintained. Because mild hypercapnia does not appear to be detrimental a fixed $F_{I_{CO_2}}$ gas source may be safer than a mecha-

nism with varying $F_{I_{CO_2}}$ and may be more quickly and easily implemented.

While the increases in CO elimination rates during hyperbaric oxygen therapy (HBO) are incontrovertible, the clinical benefit of HBO remains uncertain. HBO (at 3 ATA [atmosphere absolute]) increases the rate of CO elimination 3.5-fold compared with NBO (8), but a prospective randomized sham study of HBO versus NBO demonstrated no neurological or survival benefit of HBO (25). In addition, the observation that HbCO levels at presentation are poorly correlated with clinical manifestations suggests that the rate of CO elimination is not the only factor associated with clinical effect (26–29). The lack of consistently observed clinical benefit of HBO may be due solely to delays in initiating therapy (30). Therefore hyperventilation therapy, which eliminates CO nearly as quickly as HBO and is more readily accessible, could have a significant clinical benefit.

In conclusion, we have demonstrated up to a 2.75-fold increase in CO elimination and increases in D_{O_2} with isocapnic ventilation in an animal model of severe CO poisoning. These findings, the findings of others in animals and human volunteers, and the potentially universal access of isocapnic hyperventilation warrant further study of this therapy in CO-poisoned patients.

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