J Anesth (2007) 21:181–186
DOI 10.1007/s00540-006-0494-6

Journal of
Anesthesia

Cardiac output increases the rate of carbon monoxide elimination in hyperpneic but not normally ventilated dogs

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Abstract
Purpose. The very high solubility of carbon monoxide (CO) in blood suggests that its elimination depends predominantly on ventilation and not perfusion. Nevertheless, hyperventilation is not used for CO elimination because of the adverse effects of hypocapnia. With isocapnic hyperpnea (IH), ventilation can be increased considerably without hypocapnia. This raises the issue of whether CO elimination is limited by perfusion during IH. We studied the effect of increasing cardiac output on $t_{1/2}$, the half-time of decline of blood carboxyhemoglobin concentration ([COHb]), during normal ventilation (NV) and during IH.
Methods. After ethics approval was received, 13 pentobarbital-anesthetized ventilated dogs were exposed to CO to increase their [COHb]. They were then ventilated with NV or IH. At each level of ventilation, dogs were randomly assigned to treatment with dobutamine (to increase cardiac output) or to no dobutamine treatment. After the return of [COHb] to control levels, each dog was re-exposed to CO and treated with the same ventilatory mode, but the alternative inotropic treatment.
Results. Gas exchange, [COHb], and hemodynamic measures were recorded during the study. Cardiac index values in the IH group were 4.1 ± 0.5 and 8.2 ± 1.2 $l \cdot min^{-1} \cdot m^{-2}$ without and with dobutamine infusion, respectively. Dobutamine infusion was associated with a reduction in $t_{1/2}$ from 20.3 ± 3.6 to 16.9 ± 2.4 min ($P = 0.005$) in the IH group, but no change in the NV group.
Conclusion. These findings suggest that CO elimination during IH treatment is limited at least partly by pulmonary blood flow and may therefore be further augmented by increasing cardiac output.

Key Words Carboxyhemoglobin · Carbon monoxide · Poisoning · Isocapnic hyperpnea · Ventilation

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None of the authors have any source of support of the form of grants, gifts, equipment, or drugs.
Received: October 16, 2006 / Accepted: December 22, 2006

Introduction

Carbon monoxide (CO) poisoning is the most common cause of poisoning morbidity and mortality in the industrialized world [1]. Hyperbaric oxygenation therapy is available for severe CO poisoning. However, the delay in initiating such therapy is a serious problem, because hyperbaric chambers are relatively uncommon. As an immediately available and effective therapy for severe CO poisoning, isocapnic hyperpnea (IH), a method of maintaining isocapnia independent of the minute ventilation ($\dot{V}E$), was introduced by Fisher et al. [1] in 1999. They demonstrated that IH could reduce $t_{1/2}$, the half-time of decline of carboxyhemoglobin concentration ([COHb]), to levels comparable to those obtained with hyperbaric O_2 treatment. A subsequent study [2] in humans demonstrated that initial increases in $\dot{V}E$ were accompanied by the most dramatic reduction in $t_{1/2}$; at larger $\dot{V}E$, increments in $\dot{V}E$ resulted in progressively less reduction in $t_{1/2}$, forming a quasi-parabolic function with $t_{1/2}$ approaching an asymptote well above the baseline at a value of about 20 min. The asymptote of the parabolic function of $t_{1/2}$ vs $\dot{V}E$ represents the limitations in the pulmonary elimination of CO. The flattening of changes in $t_{1/2}$ at high $\dot{V}E$ are due to the limitation of CO diffusion from the blood into the alveoli. This limitation of diffusion may be due to a diffusion barrier posed by the tissues between the capillaries and the alveoli or it may be due to a reduction in the pulmonary capillary partial pressure of CO (P_{CO}) induced by the hyperpnea. At first glance, the latter explanation does not seem likely. As with other very highly soluble hydrocarbons, it has long been assumed that the blood capacity for CO is sufficiently high and the rate of elimination through the lung in a single pass of the blood is so low that the P_{CO} of the blood is unchanged. As such, only alveolar ventilation ($\dot{V}A$) would determine the rate of elimination of CO from the lung (and therefore the rate of the fall in blood [COHb]). However, in a

pilot study in humans, we found that IH with exercise reduced $t_{1/2}$ compared to that with IH at rest (unpublished data). This suggested that increasing cardiac output ($\dot{Q}$) could reduce $t_{1/2}$. This finding is not expected from what is understood of the pharmacokinetics of CO: CO is the equivalent of an ultra-highly soluble anesthetic, and the assumption is that its elimination should be dependent on ventilation and independent of perfusion.

Our aim was to test whether this assumption still held with IH. We hypothesized that (i) IH would be highly effective in clearing CO from the blood and (ii) that the limitation in CO elimination during IH would in fact, be perfusion-limited. If assumption (ii) is true, increasing $\dot{Q}$ during IH should further reduce $t_{1/2}$. We therefore performed a study in dogs to examine this issue further. We confirmed the effect of $\dot{Q}$ on CO elimination and provide an explanation which advances the understanding of CO pharmacokinetics.

Materials and methods

This study was approved by the Ethics Committee of the Nagoya City University Graduate School of Medical Sciences. Thirteen dogs, weighing 18–26 kg, were studied. They were anesthetized with pentobarbital, the trachea was intubated through the mouth, and the lungs were mechanically ventilated (EVA-1200; Aika, Tokyo, Japan). Adequacy of anesthetic depth was deduced from the lack of spontaneous movements and the stability of heart rate and blood pressure. Anesthesia was supplemented as necessary with the doses needed to prevent spontaneous respiratory efforts. A catheter was placed in the femoral artery for monitoring blood pressure and for the periodic sampling of blood for analysis. A thermodilution pulmonary artery catheter (Oximetrix3; Abbott, Chicago, IL, USA) was placed via the femoral vein for measuring $\dot{Q}$. The cardiac index (CI) was calculated as $\dot{Q}$ divided by body surface area, the latter calculated according to Ettinger [3]. Arterial blood was analyzed for [COHb] (OSM3 Hemoximeter; Radiometer, Copenhagen, Denmark), pH, partial pressure of CO_2 (P_{CO_2}), and P_{O_2} (ABL 505; Radiometer). Tidal gas was sampled continuously from the proximal end of the endotracheal tube and analyzed for P_{CO_2} (Capnomac Ultima; Datex–Ohmeda, Madison, WI, USA). All analog data were recorded manually.

Raising [COHb]

The initial ventilator settings were set to a tidal volume (V_T) of 15 ml·kg^{-1}, and a frequency (f) of 10 min^{-1}. V_T was adjusted in 50-ml increments as required to maintain the ventilatory response below the apneic threshold and the endtidal partial pressure of CO_2 ($P_{ET_{CO_2}}$) at 35 to 40 mmHg. After steady-state conditions were achieved (less than 2-mmHg change in $P_{ET_{CO_2}}$ over 2 min), all monitored values were recorded (control values). The dogs were then exposed to 3000 ppm (0.3%) of CO in air. [COHb] was monitored every 5 min and the exposure to CO was stopped when [COHb] was between 40% and 50%.

Protocol

After CO exposure, the first five consecutive dogs were maintained at the same ventilatory settings ("normal ventilation"; NV group) to identify the effect of an inotropic agent (dobutamine) at normal $\dot{V}E$. The remaining eight dogs were assigned to the test (IH) group. Ventilation parameters during IH were: V_T, 30 ml·kg^{-1} and f, 20 min^{-1}. Isocapnia was maintained by the method described by Sommer et al. [4]. Once the dogs were assigned to a group, they were further assigned in a random fashion to one of two treatments: 80% O_2 without inotrope (dobutamine) infusion (–I) or 80% O_2 with continuous intravenous inotrope infusion (+I). Dobutamine was initiated at 10 μg·kg^{1}·min^{1} and titrated to approximately double the $\dot{Q}$ from the values at the end of the CO exposure.

$\dot{Q}$ was measured and arterial blood sampled and analyzed for [COHb] and blood gases every 5 min for 60 min after the end of exposure to CO. After the 60-min "treatment period", IH was initiated in the NV group (and maintained in the IH group) and maintained for 60 min until [COHb] returned to the control levels. The dog was then re-exposed to CO and reassigned to the same ventilation group, but had the alternative cardiac output treatment applied. The experimental protocols are clearly outlined in Fig. 1.

Data analysis

The data from the first 7 min after treatment were excluded from the calculation in order to minimize the effect on $t_{1/2}$ of [COHb] equilibration between the various tissue compartments [5,6]. [COHb] was calculated as "measured [COHb]" minus "control [COHb]" in order to account for the effect of endogenous or residual CO in the calculation of $t_{1/2}$. The $t_{1/2}$ were calculated as $ln2/k$ from exponential curves ($y = a\,exp\,(-kt)$) (where y is [COHb] at time t, a is a constant the sum of which is equal to initial [COHb] and –k is time constant) fitted to the decay curves of [COHb] by the method of least squares. Data values are expressed as means ± SD. Welch's t-test was used to compare the values of Hb concentrations and weights of the dogs between ventilatory groups. Student's paired t-test was used to compare

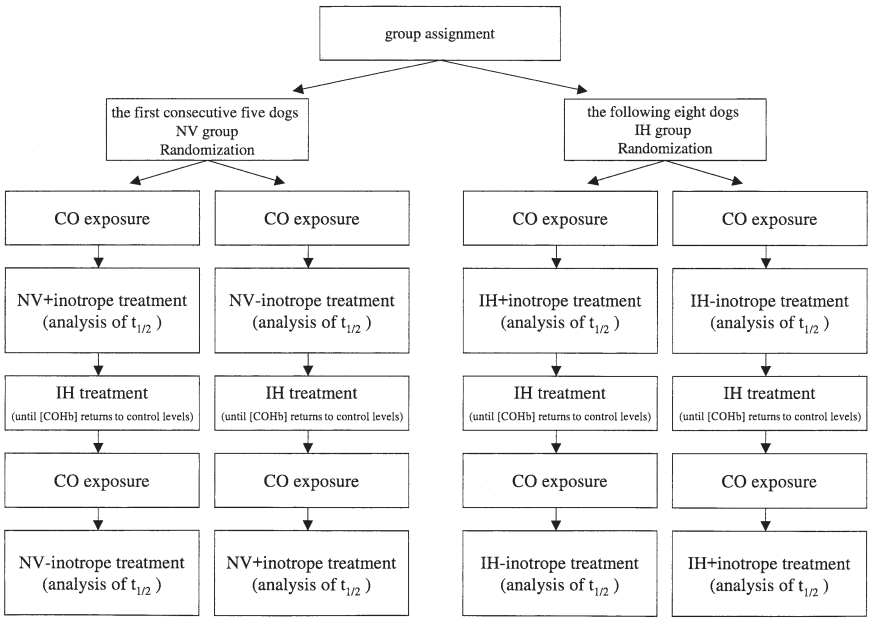

Fig. 1. Experimental protocol. Group assignment, randomization and the sequences of the different treatments a outlined. *IH treatment*, isocapnic hyperpnea (IH) treatment alone (without inotrope infusion); *NV–I treatment*, normal ventilation without inotrope infusion; *NV+I treatment*, normal ventilation with continuous intravenous inotrope infusion; *IH–I treatment*, IH treatment without inotrope infusion; *IH+I treatment*, IH treatment with continuous intravenous inotrope infusion; $t_{1/2}$, half time of decline of blood carboxyhemoglobin concentration, ([COHb])

Table 1. Normal ventilation, no dobutamine infusion

NV/–I	Weight (kg)	Hb ($g \cdot dl^{-1}$)	Pa_{CO_2} (mmHg)	Pa_{O_2} (mmHg)	Peak [COHb] (%)	CI ($l \cdot min^{-1} \cdot m^{-2}$)	$t_{1/2}$ (min)
Dog 1	20	12.5	36	437	42.0	3.7	32.9
Dog 2	21	13.0	36	457	31.9	2.1	49.2
Dog 3	19	12.8	55	463	37.1	4.9	48.5
Dog 4	21.5	14.5	30	355	29.8	6.1	55.5
Dog 5	22	13.0	40	366	33.4	4.4	38.7
Mean ± SD	20.7 ± 1.2	13.2 ± 0.8	39.4 ± 9.4	416 ± 51	33.4 ± 4.8	4.2 ± 1.5	45.0 ± 9.0
P value (vs +I)			0.79	0.66	0.2	0.003*	0.13

* $P < 0.05$ comparing the two NV treatment groups

Table 2. Normal ventilation, dobutamine infusion

NV/+I	Pa_{CO_2} (mmHg)	Pa_{O_2} (mmHg)	Peak [COHb] (%)	CI ($l \cdot min^{-1} \cdot m^{-2}$)	$t_{1/2}$ (min)
Dog 1	42	527	40.0	8.2	43.9
Dog 2	39	447	31.7	4.8	48.8
Dog 3	42	449	32.9	10.0	53.7
Dog 4	34	320	31.5	13.1	54.2
Dog 5	35	386	29.7	8.0	53.3
Mean ± SD	38.4 ± 3.8	426 ± 77	33.2 ± 4.0	8.8 ± 3.0	50.8 ± 4.4

the values of parameters other than Hb concentration and body weight between the two IH treatment groups, and between the two NV treatment groups. $P < 0.05$ was considered to be significant.

Results

In the NV group, the +I and –I cohorts had similar peak levels of [COHb] ($P = 0.20$) and arterial P_{O_2} (Pa_{O_2}, 426 ± 77 vs 416 ± 51 mmHg; $P = 0.66$). The CI in the +I group was 8.8 ± 3.0 compared to 4.2 ± 1.5 $l \cdot min^{-1} \cdot m^{-2}$ in the –I group ($P = 0.003$). Nevertheless, there was no difference in $t_{1/2}$ between the two cohorts (50.8 ± 4.4 vs 45.0 ± 9.0 min; $P = 0.13$); Tables 1 and 2.

The IH group was ventilated with a fourfold higher $\dot{V}E$ than the NV group while the Pa_{CO_2} was maintained within the target range (Tables 3 and 4). In the +I and –I cohorts of the IH group, there were no differences in peak [COHb] ($P = 0.46$) or Pa_{O_2} (448 ± 46 and 430 ±

Table 3. Isocapnic hyperpnea, no dobutamine infusion

IH/–I	Weight (kg)	Hb ($g \cdot dl^{-1}$)	Pa_{CO_2} (mmHg)	Pa_{O_2} (mmHg)	Peak [COHb] (%)	CI ($l \cdot min^{-1} \cdot m^{-2}$)	$t_{1/2}$ (min)
Dog 6	18	12.5	36.6	450	49.3	3.9	18.2
Dog 7	21	11.2	33.5	487	36.7	4.1	21.1
Dog 8	21	14.5	29.9	406	56.1	4.9	19.0
Dog 9	26	14.5	38.2	426	40.6	3.5	28.5
Dog 10	20	14.5	31.9	399	45.9	3.5	18.9
Dog 11	21	9.5	29.1	399	36.1	4.5	16.6
Dog 12	21	9.2	36.8	440	48.1	4.2	20.1
Dog 13	21	10.0	33.0	433	43.7	4.2	20.1
Mean ± SD	21.1 ± 2.2	12.0 ± 2.3	33.6 ± 3.3	430 ± 30	45 ± 7	4.1 ± 0.5	20.3 ± 3.6
P value	0.67 (vs NV)	0.37 (vs NV)	0.41 (vs IH/+I)	0.22 (vs IH/+I)	0.46 (vs IH/+I)	0.00003** (vs IH/+I)	0.005** (vs IH/+I)

** $P < 0.05$ comparing the two IH treatment groups

Table 4. Isocapnic hyperpnea, dobutamine infusion

IH/+I	Pa_{CO_2} (mmHg)	Pa_{O_2} (mmHg)	Peak [COHb] (%)	CI ($l \cdot min^{-1} \cdot m^{-2}$)	$t_{1/2}$ (min)
Dog 6	34.9	529	42.3	5.9	14.8
Dog 7	32.9	483	32.8	6.8	18.5
Dog 8	27.8	377	55.7	8.8	16.1
Dog 9	33.0	411	44.4	8.5	20.6
Dog 10	27.1	460	47.3	9.1	12.7
Dog 11	37.3	430	37.8	8.8	16.4
Dog 12	31.8	440	57.5	8.2	18.2
Dog 13	33.3	453	50.5	9.6	17.6
Mean ± SD	32.3 ± 3.4	448 ± 46	46 ± 9	8.2 ± 1.2	16.9 ± 2.4

In tables 1–4, values for $PaCO_2$, PaO_2, and cardiac index (CI) for all four treatment pattern are means of all values collected over the duration of each treatment period

30 mmHg respectively; $P = 0.22$). The values for the CI were 8.2 ± 1.2 and 4.1 ± 0.5 $l \cdot min^{-1} \cdot m^{-2}$ in the +I and –I cohorts of the IH group, respectively ($P < 0.0001$). The $t_{1/2}$ in the IH +I cohort was 16.9 ± 2.4 min compared to 20.3 ± 3.6 min in the –I cohort ($P = 0.005$); (Tables 3 and 4).

Discussion

During control ventilation, increasing the $\dot{Q}$ via inotrope infusion did not change $t_{1/2}$. Instituting IH reduced $t_{1/2}$ compared to that under control ventilation. Increasing $\dot{Q}$ by inotrope infusion during IH, reduced $t_{1/2}$ further. These findings could not be predicted with confidence from theoretical considerations arising from what is known regarding CO and its binding to Hb. It is well known that the high affinity of Hb for CO results in a large capacitance of blood for CO and a low P_{CO} [7]. As such, one could have expected that little could be gained from further lowering the alveolar P_{CO} through increased $\dot{V}A$. It was rather interesting, then, that hyperpnea, in the form of IH, markedly increased the rate of CO elimination (reduced $t_{1/2}$) to levels similar to those associated with hyperbaric oxygen therapy [1]. Even so, the pharmacokinetics would be expected to follow the principles of the elimination of highly soluble substances from the blood, i.e., being predominantly dependent on ventilation and relatively independent of perfusion [8–10]. When Takeuchi et al. [2] evaluated this principle, they found that, at higher $\dot{V}E$, some other factor—diffusion or perfusion—was limiting $t_{1/2}$. The incremental elimination of CO in response to an increase in $\dot{Q}$ in our IH group, but not in the NV group, is consistent with our hypothesis that IH reduces first-pass alveolar capillary P_{CO} and that the alveolar capillary P_{CO} is restored with increased alveolar capillary perfusion. Our findings also suggest that, under conditions of high rates of pulmonary CO elimination (such as with IH and hyperbaric O_2 treatment), increasing $\dot{Q}$ may provide additional elimination of CO.

Accelerating CO elimination

Several factors influence the rate of elimination of CO from the blood. Increasing the inspired P_{O_2} increases the

alveolar capillary P_{CO} by displacing CO from Hb. The resulting raised capillary-alveolar P_{CO} gradient results in a greater rate of diffusion of CO into the alveoli. Thus, for a given $\dot{V}A$, a greater volume of CO is eliminated. As $\dot{V}A$ increases, the alveolar P_{CO} (for a given pulmonary blood flow) is reduced, increasing the capillary-alveolar P_{CO} gradient and the diffusion of CO out of the blood. Both the increased $\dot{V}A$ and the increased rate of diffusion of CO from the capillary blood into the alveoli increase the rate of CO washout from the lung. This assumes that the level of ventilation is such that it does not substantially affect the alveolar capillary CO content and thereby the P_{CO}. This assumption is based on the principle that high blood capacitance (a term we prefer to "solubility") for CO implies that large changes of blood CO content can take place with only small changes in blood P_{CO}, maintaining the pulmonary capillary-alveolar P_{CO} gradient in the face of increases in CO elimination. The question is whether this principle holds at levels of $\dot{V}E$ seen with IH.

We also have to consider the mechanism that increasing $\dot{Q}$ accelerates the rate of CO washout from the tissue to the blood. However, increasing $\dot{Q}$ did not affect $t_{1/2}$ in our NV study. The result of the NV study suggests that $\dot{Q}$ does not affect the rate of CO washout from the tissue to the blood.

Takeuchi et al. [2] have observed that, at large $\dot{V}E$, $t_{1/2}$ becomes relatively independent of $\dot{V}E$. Our findings of a further reduction in $t_{1/2}$ brought about through increases in $\dot{Q}$ during IH suggest that the plateau of $t_{1/2}$ with hyperpnea occurs because IH reduces the blood CO content and capillary P_{CO} and that the blood P_{CO} is restored by an increase in $\dot{Q}$. This explanation is also supported by our finding that increases in $\dot{Q}$ with NV were ineffective in reducing $t_{1/2}$.

There are two additional explanations for the flattening of $t_{1/2}$ with increased $\dot{V}E$. First, at a large $\dot{V}A$, the P_{CO} gradient may already be maximal and increments in $\dot{V}A$ have little incremental effect on the gradient and thus on the rate of CO elimination. A second possible mechanism is that the diffusion across the capillary-alveolar barrier has reached a maximum rate. The reduction of $t_{1/2}$ with increased $\dot{Q}$ does not exclude a contribution from these two mechanisms; it only suggests that neither of them is sufficient to account for the limitation of CO elimination with IH.

The effect of dobutamine infusion on $t_{1/2}$ in the IH group may also have been due to the dilatation and recruitment of pulmonary capillary vessels. Dobutamine itself induces pulmonary vasodilation [11]. Pulmonary vasodilation may also be the cause of increased single-breath CO uptake by up to threefold during exercise [12]. On the other hand, we did not observe any effect of dobutamine on $t_{1/2}$ in the NV group. In the IH group, dogs were lying on their side and had a very small vertical perfusion gradation and a small zone 1 and, thus, few potential underperfused pulmonary capillaries. Nevertheless, we did not measure $\dot{V}A/\dot{Q}$ ratios and cannot completely rule out an effect of increased diffusion of CO from recruited alveoli in zone 1 of the lung.

The clinical implications of the study are that it provides the rationale for increasing $\dot{Q}$ in severely CO poisoned patients—perhaps to levels above those required for hemodynamic stability—as an aid to increase the rate of CO elimination. On the other hand, we have to take care that the myocardial ischemia induced by CO poisoning does not worsen during inotrope treatment.

Limitations of the study

In this study, each dog in each ventilatory group was its own control with respect to interventions that changed $\dot{Q}$. CO is stored not only in blood but also in tissue, and if a large quantity of CO had been retained in tissue in the first experiment, that may have affected the CO stores during the second experiment. We believe that the randomized crossover protocol controlled for this factor. In addition, before the second experiment, each dog received IH treatment for 120 min to purge the CO collected in various tissue compartments during the first experiment. We feel that this was sufficient to minimize the effect of the CO that was retained in tissues in the first experiment on the results of the second experiment. We also took into account only incremental changes in [COHb] by subtracting any initial [COHb] from the measured [COHb] during the experiment. Finally, randomization of the order of application of the dobutamine treatment would control for the persistence of residual CO from a previous experiment.

Conclusion

Hyperpnea is so effective in clearing CO from the blood that pulmonary perfusion (i.e., $\dot{Q}$) limits CO elimination. Our findings also suggest that, under conditions of maximal ventilatory elimination (such as IH and possibly hyperbaric O_2 treatment), increasing $\dot{Q}$ may further increase the rate of pulmonary CO elimination.

Acknowledgments. The authors thank the statistical expert, Sadao Suzuki, Ph.D., for review of the statistical analysis and Steve Iscoe, Ph.D., for valuable advice.

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