Increased Carbon Monoxide Clearance during Exercise in Humans

GERALD S. ZAVORSKY[1,2], JAMES M. SMOLIGA[3], LAWRENCE D. LONGO[4], KATHY A. UHRANOWSKY[1], CHRISTOPHER R. CADMAN[5], JAMES DUFFIN[6,7], and JOSEPH A. FISHER[7]

[1]Human Physiology Laboratory, Marywood University, Scranton, PA; [2]The Commonwealth Medical College, Scranton, PA; [3]Department of Physical Therapy, High Point University, High Point, NC; [4]Center for Perinatal Biology, School of Medicine, Loma Linda University, Loma Linda, CA; [5]Princeton University, Princeton, NJ; [6]Department of Physiology, University of Toronto, Toronto, CANADA; and [7]Department of Anesthesia, University Health Network, University of Toronto, Toronto, CANADA

BASIC SCIENCES

ABSTRACT

ZAVORSKY, G. S., J. M. SMOLIGA, L. D. LONGO, K. A. UHRANOWSKY, C. R. CADMAN, J. DUFFIN, and J. A. FISHER. Increased Carbon Monoxide Clearance during Exercise in Humans. *Med. Sci. Sports Exerc.*, Vol. 44, No. 11, pp. 2118–2124, 2012. **Purpose**: Hyperventilation increases the clearance of carbon monoxide (CO) from blood; thus, we hypothesized that CO elimination would be enhanced with exercise. Accordingly, this study examined the effect of exercise on the half-life of carboxyhemolobin elimination. **Methods**: Six healthy subjects (three males and three females) with mean ± SD ages of 23 ± 4 yr were exposed to CO sufficient to raise blood carboxyhemolobin concentration to 10–14% on five separate days. The half-life for CO elimination was measured breathing room air at rest and during exercise at three intensities. **Results**: Comparisons showed that the half-life decreased with exercise from that during rest in all subjects. The half-life was also measured during 100% oxygen breathing at the lowest exercise intensity of 63 ± 15 W and found to be the least of all measured (23 ± 4 min). **Conclusions**: 1) Exercise increased isocapnic ventilation, thereby decreasing the half-life of CO elimination. 2) The half-life of CO elimination represents a hyperbolic function of ventilation [$y = y0 + (a / x)$], and so increasing ventilation by exercise reaches a point of diminishing returns. 3) Breathing 100% oxygen during mild exercise is as effective in eliminating CO as treatment with hyperbaric oxygen. 4) Moderate exercise under room air conditions is as effective in eliminating CO as breathing oxygen at rest. Thus, the combination of mild exercise, hyperventilation, and normobaric hyperoxia (100% oxygen inhalation) may be considered the "triple therapy" for CO elimination in some patients. **Key Words:** CARBOXYHEMOGLOBIN, COHb DECAY, CARBON MONOXIDE WASHOUT, PHARMACOKINETICS, CYCLING

Carbon monoxide (CO) is a poisonous, odorless, colorless gas that is highly soluble in blood. In humans, CO reduces hemoglobin's oxygen (O_2)-carrying capacity (4) and is toxic for mitochondria by altering the mitochondrial respiratory chain at the cytochrome c oxidase level (1) (see Refs. [10,19] for reviews). The incidence of unintentional, non–fire-related CO exposures in the United States is 6.2 per 100,000 people (5). Eighty percent of those exposures occur in the individual's place of residence (5), with the source of CO attributed mainly to malfunctioning nonelectric heaters (i.e., coal heaters, wood heaters, and gas heaters) and cooking equipment. About 15% had exposure symptoms that were pronounced, prolonged, or systemic and usually required treatment (5). A further 2% had symptoms that were life threatening or resulted in significant disability (5).

Current treatment is directed, first at increasing the O_2 delivery to the tissues by maximizing the volume of O_2 dissolved in the plasma and, second, to optimizing the rate of dissociation of CO from hemoglobin, both achieved by normobaric hyperoxia. Still, breathing 100% O_2 at 1 atm increases the rate of CO elimination by a factor of 4–5 at sea level (20) and further by a another factor of 3 at 2.5–3.0 atm, shortening the mean half-time ($t_{1/2}$) of reduction of carboxyhemoglobin concentration ([COHb]) to 15–23 min (11,12), compared with 3–5 h while breathing room air at rest (11,12). Although the clinical efficacy of hyperbaric oxygen treatment is in doubt (2,14), it is nevertheless recommended (if available) for pregnant patients and those with cardiac and severe neurological symptoms.

In 1959, Killick and Marchant (8) pointed out that the increases in CO elimination produced by the addition of carbon dioxide (CO_2) in hyperoxia were due not to the CO_2 itself but to the CO_2-induced increase in ventilation. A half century later, Takeuchi et al. (16) showed that $t_{1/2}$ decline

Address for correspondence: Gerald S. Zavorsky, Ph.D., 2300 Adams Avenue, Marywood University, Scranton, PA 18509; E-mail: zavorsky@marywood.edu.
Submitted for publication February 2012.
Accepted for publication May 2012.

0195-9131/12/4411-2118/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/MSS.0b013e3182602a00

is a hyperbolic[1] function of minute ventilation (a rectangular hyperbola). They also showed that isocapnic, normobaric, hyperoxic hyperventilation reduced [COHb] as effectively as hyperbaric O_2 (16). Rucker et al. (13) showed that administration of hyperoxia alone resulted in hyperventilation, hypocapnia, and reduced cerebral oxygen delivery. They showed that normocapnia can be maintained during hyperpnea by compensating for the increased alveolar ventilation by adding a complementary volume of about 5% CO_2 to inspired gas (16). However, there is an alternative to adding inspired CO_2 to maintain normocapnia: exercise. During relatively moderate exercise (ventilation rate = 65 to 70 $L \cdot min^{-1}$), arterial carbon dioxide partial pressure is maintained at normocapnic levels (40 mm Hg) because ventilation is closely matched to the CO_2 production (18,22).

We therefore hypothesized that exercise would increase the elimination of CO proportionate to the exercise load. This study was designed to test this hypothesis by measuring $t_{1/2}$ in healthy subjects breathing room air at rest (normoxia) and at various exercise intensities. We also measured the $t_{1/2}$ in subjects engaging in mild exercise while inspiring 100% O_2, and hypothesized that CO elimination would be maximized under these conditions.

METHODS

Study Design

The study was approved by the Institutional Review Board of Marywood University, and all subjects provided their written informed consent before the start of the study. The sample size calculation was estimated to be five subjects based on the paired differences in $t_{1/2}$ at rest (20) compared with a mild ventilation rate of about 500 $mL \cdot kg^{-1} \cdot min^{-1}$ (16) (substituted for exercise). However, a convenience sample of nine subjects (five males) who were physically active, who were nonsmokers, and who had no known clinical illness and normal hemoglobin levels (women >12.2 $g \cdot dL^{-1}$, men >13.7 $g \cdot dL^{-1}$) (3) was recruited to participate in this study. The added subjects recruited were to ensure that at least five subjects completed the study. Subjects were recruited via postings around the university campus between April and September 2011. Each subject participated in six testing sessions on separate days for a period of 3 wk.

Methods and Measurements

Session 1: Cardiopulmonary exercise test to determine aerobic capacity and exercise intensities. A 5-min average of resting oxygen uptake ($\dot{V}O_{2rest}$) and resting HR while sitting upright was obtained before the cardiopulmonary exercise test. Maximal oxygen consumption ($\dot{V}O_{2max}$) was assessed using an electrically braked cycle ergometer (Velotron Dynafit Pro; Racermate Inc., Seattle, WA). The cardiopulmonary exercise test began at 30 to 40 W and increased by 30 W every 2 min in a stepwise fashion until volitional exhaustion. The cardiopulmonary variables $\dot{V}O_2$ and ventilation ($\dot{V}_E$) were measured with a metabolic cart (Sensormedics VMAX 229D; Viasys Healthcare, Palm Springs CA). The mean of the highest three consecutive $\dot{V}O_2$ values averaged over 20-s intervals was defined as $\dot{V}O_{2max}$. Heart rate (HR) was recorded using a Polar HR monitor (Polar Electro Oy, Kempele, Finland).

From the measured resting $\dot{V}O_2$ and $\dot{V}O_{2max}$, three target exercise intensities were calculated for each subject for the remaining sessions at about 40%, 50%, and 70% of their individual oxygen uptake reserve ($\dot{V}O_2R$). The $\dot{V}O_2$ at each percentage $\dot{V}O_2R$ was calculated by multiplying the desired percentage (as a fraction) by ($\dot{V}O_{2max} - \dot{V}O_{2rest}$) and adding the $\dot{V}O_{2rest}$ in liters per minute. Once the O_2 was calculated for each intensity, the predicted power output was calculated to match the $\dot{V}O_2R$ using a linear regression between $\dot{V}O_2$ and power output (W) for each subject from the cardiopulmonary exercise test.

Sessions 2 to 6. Sessions 2 to 6 were randomized to one of the five conditions: rest, 40%, 50%, and 70% $\dot{V}O_2R$ during normoxia and 40% $\dot{V}O_2R$ breathing 100% O_2. At the beginning of these sessions, a 20-G intravenous catheter was inserted aseptically into a forearm vein of the subject and kept patent by a slow intravenous drip of normal saline. After aspirating the dead space fluid from the catheter, blood samples were drawn into in a heparinized syringe (Portex® 3-mL line draw syringe; Smiths Medical, Keene, NH). All blood samples were measured by a blood–gas analyzer and immediately analyzed for measurements of venous blood hemoglobin concentration and COHb percentage (ABL80 FLEX Co-oximeter; Radiometer, Copenhagen, Denmark). Blood measurements were also made at baseline.

At the beginning of the study, subjects were asked to periodically inhale to total lung capacity from a 5-L anesthesia bag containing a mixture of 0.3% CO, 10% He, 21% O_2, and Bal N_2 and then rebreathe this gas for about 10 to 14 breaths lasting about 10 s each. This was repeated 10–14 times, separated by 20-s rest intervals until [COHb] reached 10% to 14%. The [COHb] was measured after every fifth set of rebreathe maneuvers, with blood being drawn after a 3-min stabilization period. This on-gassing procedure took 20 to 30 min. Then, exercise at room air or 100% O_2 commenced. Blood samples were obtained approximately every 10 to 20 min under normoxia and every 5 min under hyperoxia. Sampling continued until [COHb] decreased to half of its initial value. HR, $\dot{V}O_2$, and $\dot{V}_E$ were monitored throughout the session. All cardiopulmonary data and [COHb] values were collected and recorded using commercial data acquisition software.

Primary Data Analysis

For each test, [COHb] versus time was fitted with an exponential decay using a Levenberg–Marquardt fitting

[1]Sigmaplot 11.2 (Systat Software Inc., San Jose, CA) actually defines this hyperbolic function as $y = y0 + (a/x)$, which falls under the polynomial equation category as an inverse first-order equation for that software.

technique to determine $t_{1/2}$. Then, for each subject, the relation between $t_{1/2}$ from the normoxic rest and the three exercise loads and $\dot{V}_E$ normalized for body weight was fitted with a hyperbolic function[2] using a Levenberg–Marquardt fitting technique. Curve fitting for each individual was performed using custom-written software (LabVIEW; National Instruments, Austin, TX). Curve fitting for the group was performed using Sigmaplot 11.2 (Systat Software Inc., Chicago, IL).

Descriptive statistics are reported as means and SDs. A one-way repeated-measures ANOVA was used to determine whether there were differences in $t_{1/2}$ between the different conditions (SPSS Version 19.0; SPSS Inc., Chicago, IL). Similar tests were used to determine whether there were mean differences in other cardiopulmonary parameters ($\dot{V}O_2$, $\dot{V}_E$, HR, and power output) between the four different levels of oxygen consumption. When a main effect was present, Tukey pairwise comparisons were used to identify differences between specific conditions. For comparison of $t_{1/2}$ with those previously reported by another group, *t*-tests were used.

To determine which factors affect $t_{1/2}$ during exercise, we also performed multiple regression analyses using the data obtained from the three exercise intensities (40%, 50%, and 70% $\dot{V}O_2R$) while subjects breathed room air. The independent variables were $\dot{V}O_2$ ($L \cdot min^{-1}$), $\dot{V}_E$ ($L \cdot min^{-1}$), weight (kg), age (yr), height (cm), and sex (1 = male, 0 = female) as independent variables. A stepwise model was used to determine which dependent variables most contributed to $t_{1/2}$ during exercise. The probability of *F* to enter was set at 0.05, and the probability of *F* to remove was set at 0.10. Standardized coefficients were computed to determine the final model. The multiple regression analyses was performed using SPSS Version 19.0 (SPSS Inc., Chicago, IL).

RESULTS

Six subjects (three males) completed all of the testing sessions, whereas another three subjects completed two or fewer of the five sessions. No subjects experienced any adverse events during this study or had had any symptoms of CO poisoning. The anthropometric characteristics of the subjects and their peak values from the cardiopulmonary exercise tests are presented in Table 1. Table 2 presents the $t_{1/2}$ corresponding to the measured $\dot{V}O_2R$ (rest, then 40%, 50%, and 70%). The mean peak [COHb] for the six completed subjects was 10.9% ± 0.8% for all sessions. The mean day-to-day SD in peak [COHb] for the five sessions per subject was 0.6%. Exercise intensity affected all variables listed in Table 2 under normoxia ($P < 0.001$, observed power ≥0.90 for all). The $t_{1/2}$ (mean ± SD) at 40% $\dot{V}O_2R$ under 100% O_2 inhalation (23.2 ± 3.5 min) was markedly less than that at the same workload breathing room air (100.5 ± 16.5, $P < 0.001$, observed power = 1.00). HR did not differ between subjects who were normoxic versus those that were hyperoxic.

[2]The function is described as $y = y0 + (a/x)$.

TABLE 1. Anthropometric characteristics and peak values from the cardiopulmonary exercise test.

n = 9	Mean ± SD	Range
Age (yr)	23 ± 4	21–32
Mass (kg)	66.1 ± 12.0	46.7–80.3
Height (cm)	169 ± 12	151–184
BMI ($kg \cdot m^{-2}$)	23.5 ± 2.6	17.1–26.6
[COHb] baseline (%)	1.3 ± 0.2	1.0–1.8
Hemoglobin ($g \cdot dL^{-1}$)	13.5 ± 0.7	12.5–14.9
$\dot{V}O_{2max}$ ($L \cdot min^{-1}$)	3.0 ± 0.6	2.19–4.0
$\dot{V}O_{2max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	45.5 ± 5.2	36.6–52.5
$\dot{V}O_{2max}$ ($L \cdot min^{-1} \cdot m^{-2}$)	1.72 ± 0.21	1.41–2.07
RER_{max}	1.19 ± 0.08	1.07–1.32
$\dot{V}_{Emax}$ ($L \cdot min^{-1}$)	101 ± 20	76–135
$\dot{V}_{Emax}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	1491 ± 173	1183–1687
$\dot{V}_{Emax}$ ($L \cdot min^{-1} \cdot m^{-2}$)	56.2 ± 7.0	45.7–66.5
HR_{max} ($beats \cdot min^{-1}$)	188 ± 7	176–198
Power output at maximum exercise (W)	206 ± 43	140–260

BMI, body mass index.

Figure 1 presents the CO elimination data from one subject with the exponential decay fits. The mean ± SD (max–min) r^2 values for these fits were 0.985 ± 0.013 (0.999–0.948). The mean ± SD $t_{1/2}$ for CO elimination as well as other measures for each condition is shown in Table 2.

The relation between $t_{1/2}$ and $\dot{V}_E$ and between $t_{1/2}$ and $\dot{V}O_2$ under room-air conditions is shown in Figure 2. A comparison between the $t_{1/2}$ for all conditions with repeated-measures ANOVA is shown in Figure 3.

We used the prediction equation from Takeuchi et al. (16) to compare the $t_{1/2}$ during O_2 breathing exercise at 30% O_2 uptake reserve with values obtained during isocapnic O_2 breathing at rest. The equation used the ventilations of our subjects during O_2 breathing exercise at 30% O_2 uptake reserve to predict $t_{1/2}$ during O_2 breathing at rest ($t_{1/2} = 21 + 5059 / \dot{V}_E$). A *t*-test comparison showed that the exercise $t_{1/2}$ (23.2 ± 3.5 min) was less than that at rest (29.9 ± 0.9 min, $P < 0.001$). Figure 4 shows this comparison.

To further reduce the SEE of the function, we removed the resting data and used only the exercise data for normoxia from the linear part of the curve. Using stepwise multiple linear regression, $\dot{V}_E$ was the first variable entered into the model, resulting in a significant model (adjusted $r^2 = 0.22$, $F(1,18) = 6.2$, $P = 0.023$). This revealed that $\dot{V}_E$ was the best individual predictor of $t_{1/2}$. The stepwise procedure then entered body mass into the model, and no further variables (age, height, gender, and $\dot{V}O_2$) met the criteria for entry. The final multiple linear regression indicated an overall model using two factors (out of six) that best predicted $t_{1/2}$ (adjusted $r^2 = 0.779$, SEE = 8.6 min, $F(2,17) = 34.6$, $P < 0.001$, Durbin–Watson = 2.18, tolerance = 0.69):

Equation for exercise normoxia only:

$$t_{1/2} = 1.39\ (\text{body mass}) - 1.17\dot{V}_E + 47.5$$

where $t_{1/2}$ is in minutes, body mass is in kilograms, and $\dot{V}_E$ is in liters per minute.

Given that there were two predictors and 20 data points in this regression equation, the 95% confidence interval (CI) for the adjusted r^2 was found to be 0.63 to 0.93. The 95% CI for

TABLE 2. Carboxyhemoglobin decay at various exercise intensities.

Variable (n = 6)	21% FIO_2				100% FIO_2
Measured intensity (% $\dot{V}O_2R$)	Rest	40% (6%)	50 (9%)	70% (10%)	40% (6%)
[COHb]$t_{1/2}$ (min)[a,c,d]	287.0 ± 56.5 [220.4–360.0] (227.4–345.9)	100.1 ± 15.5 [80.0–122.2] (83.8–116.5)	86.8 ± 14.1 [70.0–110.0] (72.0–101.7)	68.0 ± 8.6 [57.0–80.0] (59.0–77.0)	23.2 ± 3.5 [20.0–30.0] (19.5–26.9)
Watts[b–d]	0	63 ± 15 [45–80] (47–79)	96 ± 20 [75–120] (75–117)	135 ± 24 [100–155] (110–160)	63 ± 15 [45–80] (45–79)
$\dot{V}O_2$ (mL·kg^{-1}·min^{-1})[c,d]	4.3 ± 0.6 [3.5–5.4] (3.6–4.9)	20.7 ± 2.0 [17.9–22.4] (18.6–22.8)	24.9 ± 3.2 [21.0–30.4] (21.6–28.3)	33.2 ± 3.1 [29.4–37.9] (30.0–36.5)	–
$\dot{V}O_2$ (L·min^{-1})[c,d]	0.29 ± 0.09 [0.18–0.41] (0.19–0.38)	1.35 ± 0.29 [0.98–1.80] (1.05–1.66)	1.67 ± 0.48 [1.10–2.45] (1.16–2.17)	2.18 ± 0.40 [1.76–2.69] (1.76–2.59)	–
$\dot{V}O_2$ (L·min^{-1}·m^{-2})[b,c]	0.16 ± 0.03 [0.12–0.21] (0.13–0.19)	0.79 ± 0.08 [0.67–0.89] (0.70–0.86)	0.94 ± 0.15 [0.75–1.21] (0.79–1.11)	1.25 ± 0.07 [1.20–1.35] (1.18–1.33)	–
$\dot{V}_E$ (mL·kg^{-1}·min^{-1})[b–d]	142 ± 14 [132–169] (127–157)	517 ± 62 [412–603] (453–581)	670 ± 103 [575–856] (562–778)	926 ± 102 [786–1033] (819–1034)	576 ± 61 [512–641] (512–640)
$\dot{V}_E$ (L·min^{-1})[c,d]	9.4 ± 2.3 [6.2–13.0] (7.0–11.9)	34.2 ± 9.3 [24.2–48.6] (24.6–44.0)	44.6 ± 13.9 [28.0–68.9] (30.0–59.2)	60.6 ± 11.8 [47.3–80.2] (48.2–73.0)	37.6 ± 6.4 [29.8–49.0] (30.8–44.3)
$\dot{V}_E$ (L·min^{-1}·m^{-2})[b–d]	5.4 ± 0.8 [4.2–6.7] (4.5–6.2)	19.8 ± 2.9 [16.6–24.0] (16.8–22.8)	25.7 ± 5.1 [19.2–34.1] (20.3–31.1)	34.9 ± 3.0 [32.4–39.7] (31.7–38.0)	21.7 ± 1.9 [19.7–24.2] (19.7–23.6)
HR (beats·min^{-1})[b–d]	64 ± 13 [44–79] (51–77)	115 ± 16 [98–143] (98–132)	138 ± 14 [126–155] (124–152)	158 ± 10 [144–170] (147–169)	107 ± 16 [96–138] (90–123)

The data are presented as mean ± SD unless stated otherwise. The data in brackets indicate range. The data in parentheses indicate 95% CI. All exercise conditions were significantly different from rest. Statistical significance was based on Bonferroni adjustments ($P < 0.05$). Other cardiopulmonary variables are reported as well. According to the Haldane transformation, oxygen consumption cannot be measured when inspiring 100% oxygen because the fraction of inspired nitrogen is zero. However, oxygen consumption is expected to be similar compared with normoxia because the workload was kept the same between the two conditions.

[a] Significant difference between 40% normoxia versus 40% hyperoxia.
[b] Significant difference between 40% versus 50%.
[c] Significant difference between 40% versus 70%.
[d] Significant difference between 50% versus 70%.

the slope of $\dot{V}_E$ was −1.48 to −0.85, and for weight, the 95% CI for the slope was 1.0 to 1.8. Specifically, 56% of the variance in $t_{1/2}$ was accounted for body by mass, whereas 22% of the variance in $t_{1/2}$ was accounted for by $\dot{V}_E$ during exercise. Body mass, and therefore total body CO content, was the strongest predictor of $t_{1/2}$ between individuals. However, within an individual, $\dot{V}_E$ during exercise was the strongest predictor of $t_{1/2}$. This is further supported in that partial correlation relating $\dot{V}_E$ to $t_{1/2}$, controlling for body mass, revealed a strong negative association ($r = -0.88$, $P < 0.001$), indicating that a greater $\dot{V}_E$ is associated with a reduced $t_{1/2}$ for a given body mass.

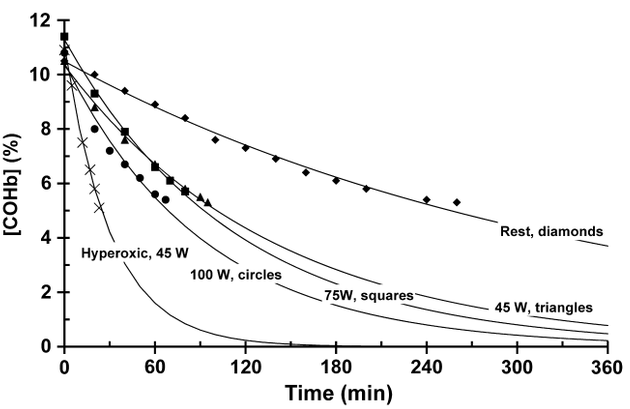

FIGURE 1—[COHb] elimination over time for one subject under various conditions. Room air breathing at rest (*diamonds*) and at exercise (45 W (*triangles*), 75 W (*squares*), and 100 W (*circles*)) and inhaling 100% O_2 at 45 W. The lines show the Levenberg–Marquardt fits determining the $t_{1/2}$ for [COHb] elimination in each condition.

DISCUSSION

General. The primary purpose of this study was to test the hypothesis that exercise would increase the clearance of carbon monoxide (CO) from blood compared with the resting state. This hypothesis was based on the known increased CO elimination provided by hyperventilation, with isocapnia maintained by added inspired CO_2 (16). In this

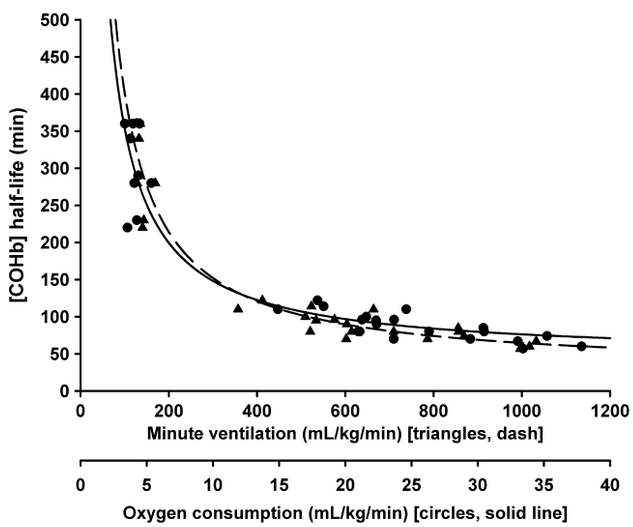

FIGURE 2—The $t_{1/2}$ as a function of minute ventilation (*triangles*) and oxygen consumption (*circles*) under normoxia during rest and exercise. The 29 data points per curve were obtained from >300 venous blood samples. *Dashed line*: $t_{1/2} = 27.1 + [37{,}466(1 / \dot{V}_E)]$, adjusted $r^2 = 0.93$, SEE = 28.4 min, $F(1,27) = 367$, $P < 0.001$. *Solid line*: $t_{1/2} = 45.5 + [1027(1 / \dot{V}O_2)]$, adjusted $r^2 = 0.90$, SEE = 34.5 min, $F(1,27) = 242$, $P < 0.001$.

study, we used exercise to increase ventilation, whereas isocapnia was maintained by the exercise-induced increased CO_2 production (18). In the present study, the half-life of CO elimination was reduced significantly by exercise while breathing air. Also, increasing the exercise load above 30% of oxygen uptake reserve offered little benefit in the rate of reduction in [COHb].

At rest, $t_{1/2}$ was 4.8 h, which is within the reported range of 3.0 to 5.3 h measured experimentally in humans (11,15). Mild exercise reduced $t_{1/2}$ to one-third of this value. And breathing pure oxygen during the mildest exercise reduced the half-life still further to its lowest value of mean ± SD = 23 ± 4 min. This $t_{1/2}$ is significantly lower than that measured in a similar group of subjects using isocapnic hyperventilation at rest to speed the elimination of CO (16) (Fig. 4) and similar to $t_{1/2}$ in hyperbaric oxygen at 2.5 to 3.0 atm (11,15). Indeed, it is shorter than the $t_{1/2}$ reported for the standard treatment of CO poisoning with oxygen, which ranged from 26 to 148 min (mean ± SD = 74 ± 25 min in one study [20]). Another study also reported half-lives that were longer: 92 ± 40 min for mechanically ventilated fire victims and 87 ± 37 min for spontaneously breathing subjects (9).

Why might the $t_{1/2}$ we observed during hyperoxic exercise be about 7 min less than that observed for a similar group of subjects, isocapnically hyperventilating to the same degree, but at rest (Fig. 4) (16)? A possible explanation is the increase of cardiac output in exercise that does not occur at rest, which would bring more CO to the lung that can be washed out by the high ventilation. Cardiac output increases little with hyperpnea (17), at a ventilation of 802 $mL \cdot kg^{-1} \cdot min^{-1}$ (60 $L \cdot min^{-1}$); cardiac output increases only by approximately 1 $L \cdot min^{-1}$ from that at rest. Because the decrease of the $t_{1/2}$ with increasing ventilation reaches an asymptotic value that is not zero, we suggest that this limitation may result from the delivery of CO to the lungs; that is, it is cardiac output dependent. At high minute ventilations, the partial pressure of CO in the alveoli is maintained so low, and the transfer of CO from the capillary blood is so high that the partial pressure of CO in the capillary blood is reduced. At that point, the CO elimination starts to become perfusion limited. Exercise then increases blood flow to the alveoli and maintains a high partial pressure gradient, optimizing the rate of CO clearance through the lung. Thus, the increased cardiac output of exercise may reduce the asymptotic value that the half-life approaches at high ventilations. When we jointly analyze the data from Takeuchi et al. (16), we find that approximately 80% of the change in $t_{1/2}$ in our study is due to increased $\dot{V}_E$ whereas the remaining approximately 20% results from other factors, presumably the chief of which is increased cardiac output (6.7 min / 30.0 min = 0.22). In other words, at that level of $\dot{V}_E$, CO elimination, on average, is 80% dependent on $\dot{V}_E$, and up to 20% may be dependent on cardiac output, reflecting the extent of limitation due to perfusion. In support of our hypothesis, Ishida et al. (7) demonstrated, in a dog model, some dependence of CO elimination half-life on cardiac output at high ventilations. Pulmonary capillary dilation and recruitment are enhanced with augmented cardiac output but not with augmented ventilation. For every liter per minute increase in cardiac output, there is a 7- to 16-mL increase in pulmonary capillary blood volume along with an increase of approximately 1.5 to 1.7 $mL \cdot min^{-1} \cdot mm\ Hg^{-1}$ in pulmonary diffusing capacity for CO and a approximately 1 to 2.5 $mL \cdot min^{-1} \cdot mm\ Hg^{-1}$ increase in alveolar-membrane diffusing capacity for CO (measured from rebreathing maneuvers) (6,21). In fact, when matched to the same exercising $\dot{V}O_2$ in this study, pulmonary diffusing capacity for CO increases by approximately 28% from rest (21). Thus, the increased pulmonary vasodilation triggered by the rise in cardiac output enhances pulmonary diffusing capacity, which may contribute to $t_{1/2}$.

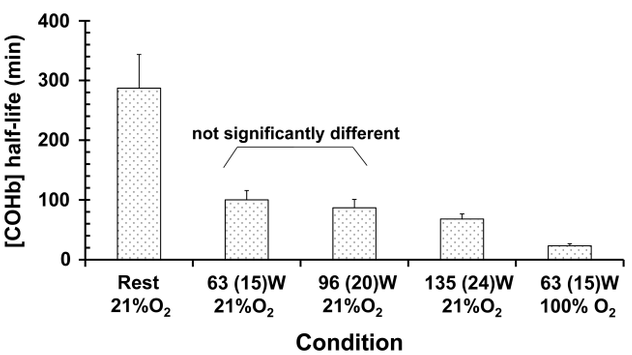

FIGURE 3—$t_{1/2}$ for all subjects and conditions. Exercise levels are shown as mean ± SD (W). The inspired oxygen concentration is shown in percentage.

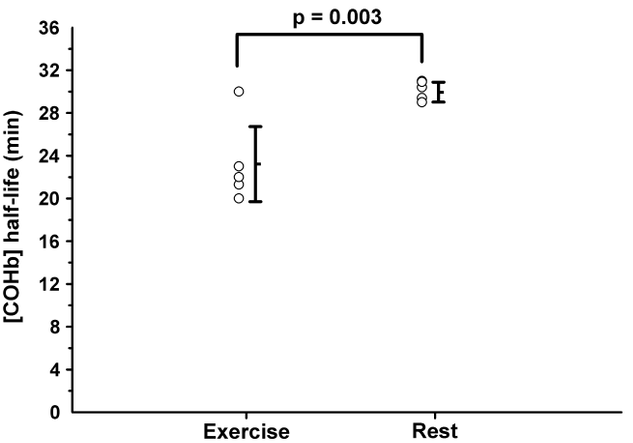

FIGURE 4—The comparison between $t_{1/2}$ obtained in this present study using light exercise (63 W) versus the predicted $t_{1/2}$ from Takeuchi et al. (16) without exercise, matched for the same $\dot{V}_E$ and 95% to 100% O_2 supplementation. The *circles* represent the actual and matched data. The *whiskers* represent the mean and SD. $t_{1/2}$ from Takeuchi = 21 + [5059 (1 / $\dot{V}_E$)], adjusted r^2 = 0.87, SEE = 9.9 min, $F(1,14) = 103$, $P < 0.001$.

Clinical implications. The hyperbolic relation between the half-life of CO elimination and ventilation (Fig. 2) means that increasing ventilation either by voluntary hyperventilation or the increased ventilation of exercise brings little advantage above a certain value. Therefore, only a moderate increase in exercise-induced ventilation is necessary and should be easily achievable either voluntarily or with mechanical ventilation.

If our theory of cardiac output limitation is correct, then this factor is an important consideration in patients with the most severe CO poisoning because they also experience severe cardiovascular depression; they will therefore have the greatest limitation in the efficacy of CO treatment with hyperoxia and hyperpnea. Although an exercise-induced increase in cardiac output may not be therapeutically feasible in such patients, our study provides a rationale for considering the use of cardiovascular stimulation with inotropic drugs as an adjuvant to boost CO clearance. By contrast, in the majority of patients with CO exposures that are not systemically ill (5), there may be a therapeutic role for exercise. Selected patients in the field, such as fire fighters and soldiers, who are exposed to large CO concentrations, could benefit by adding a component of voluntarily increased physical activity. Thus, "triple therapy," exercise, hyperventilation, and normobaric hyperoxia, could be the future gold standard for CO removal in these patients.

Limitations. Only one hyperoxic exercise was tested at the lowest load rather than repeating the test at the other exercise levels where room air was breathed. This single level of exercise was chosen to allow comparison of the results to those from Takeuchi et al. (16), thereby minimizing the exposure of our subjects to CO and the inconvenience and discomfort of the experimental protocol.

CONCLUSIONS

We have shown that air-breathing exercise is more effective in accelerating CO elimination than air breathing at rest. Performing light exercise is almost as effective as the current CO treatment of breathing 100% oxygen at rest. Performing moderate exercise is as effective as the current CO treatment of breathing 100% oxygen at rest. Breathing 100% oxygen during light exercise (63 W) reduces $t_{1/2}$ to 23 min, equivalent to that achieved in hyperbaric oxygen. Thus, the combination of mild exercise, hyperventilation, and normobaric hyperoxia (100% oxygen inhalation) may one day be considered the "triple therapy" for CO elimination in some patients.

J.A. Fisher and J. Duffin are members of a team that developed a device for clearance of carbon monoxide. However, this device is *not* used in this manuscript.

The authors would like to thank Marywood University (Murray Award) for funding this study. Portions of these data were presented as an abstract at the 2011 Canadian Society for Exercise Physiology National Conference (Quebec City, October 19 to 22, 2011). The abstract was titled "The use of exercise to remove carbon monoxide from blood."

No other coauthor has a conflict of interest.

These results do not constitute endorsement by the American College of Sports Medicine.

REFERENCES

1. Alonso JR, Cardellach F, Lopez S, Casademont J, Miro O. Carbon monoxide specifically inhibits cytochrome c oxidase of human mitochondrial respiratory chain. *Pharmacol Toxicol*. 2003;93(3): 142–6.
2. Annane D, Chadda K, Gajdos P, Jars-Guincestre MC, Chevret S, Raphael JC. Hyperbaric oxygen therapy for acute domestic carbon monoxide poisoning: two randomized controlled trials. *Intensive Care Med*. 2011;37(3):486–92.
3. Beutler E, Waalen J. The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration? *Blood*. 2006;107(5):1747–50.
4. Brody JS, Coburn RF. Carbon monoxide–induced arterial hypoxemia. *Science*. 1969;164(885):1297–8.
5. Bronstein A, Clower JH, Iqbal S, et al. Carbon monoxide exposures—United States, 2000–2009. *MMWR Morb Mortal Wkly Rep*. 2011;60:1014–7.
6. Hsia CCW, McBrayer DG, Ramanathan M. Reference values of pulmonary diffusing capacity during exercise by a rebreathing technique. *AM J Respir Crit Care Med*. 1995;152:658–65.
7. Ishida S, Takeuchi A, Azami T, et al. Cardiac output increases the rate of carbon monoxide elimination in hyperpneic but not normally ventilated dogs. *J Anesth*. 2007;21(2):181–6.
8. Killick EM, Marchant JV. Resuscitation of dogs from severe acute carbon monoxide poisoning. *J Physiol*. 1959;147:274–98.
9. Levasseur L, Galliot-Guilley M, Richter F, Scherrmann JM, Baud FJ. Effects of mode of inhalation of carbon monoxide and of normobaric oxygen administration on carbon monoxide elimination from the blood. *Hum Exp Toxicol*. 1996;15(11):898–903.
10. Longo LD. The biological effects of carbon monoxide on the pregnant woman, fetus, and newborn infant. *Am J Obstet Gynecol*. 1977;129(1):69–103.
11. Pace N, Strajman E, Walker EL. Acceleration of carbon monoxide elimination in man by high pressure oxygen. *Science*. 1950; 111(2894):652–4.
12. Peterson JE, Stewart RD. Absorption and elimination of carbon monoxide by inactive young men. *Arch Environ Health*. 1970; 21(2):165–71.
13. Rucker J, Tesler J, Fedorko L, et al. Normocapnia improves cerebral oxygen delivery during conventional oxygen therapy in carbon monoxide–exposed research subjects. *Ann Emerg Med*. 2002;40(6):611–8.
14. Scheinkestel CD, Bailey M, Myles PS, et al. Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: a randomised controlled clinical trial. *Med J Aust*. 1999;170(5): 203–10.
15. Stewart RD, Peterson JE, Baretta ED, Bachand RT, Hosko MJ, Herrmann AA. Experimental human exposure to carbon monoxide. *Arch Environ Health*. 1970;21(2):154–64.

16. Takeuchi A, Vesely A, Rucker J, et al. A simple "new" method to accelerate clearance of carbon monoxide. *Am J Respir Crit Care Med*. 2000;161(6):1816–9.
17. Vogiatzis I, Athanasopoulos D, Habazettl H, et al. Intercostal muscle blood flow limitation in athletes during maximal exercise. *J Physiol*. 2009;587(Pt 14):3665–77.
18. Wasserman K, Beaver WL, Sun XG, Stringer WW. Arterial H+ regulation during exercise in humans. *Respir Physiol Neurobiol*. 2011;178(2):191–5.
19. Weaver LK. Carbon monoxide poisoning. *Crit Care Clin*. 1999; 15(2):297–317, viii.
20. Weaver LK, Howe S, Hopkins R, Chan KJ. Carboxyhemoglobin half-life in carbon monoxide–poisoned patients treated with 100% oxygen at atmospheric pressure. *Chest*. 2000;117(3): 801–8.
21. Zavorsky GS, Beck KC, Cass LM, Artal R, Wagner PD. Dynamic vs. fixed bag filling: impact on cardiac output rebreathing protocol. *Respir Physiol Neurobiol*. 2010;171(1):22–30. Erratum in: *Respir Physiol Neurobiol*. 2012; 80(2–3):353–4.
22. Zavorsky GS, Lands LC, Schneider W, Carli F. Comparison of fingertip to arterial blood samples at rest and during exercise. *Clin J Sport Med*. 2005;15(4):263–70.