



# **Prediction of the Consequences of Endogenous Carbon Monoxide Production During an Extravehicular Activity in Microgravity**

*Eugene N. Bruce, Ph. D.  
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*Work completed for NASA under a subcontract through Universities Space Research  
Association: NNJ11HE31A, PN 02.106.001.*

National Aeronautics and  
Space Administration

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Houston, Texas 77058*

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## ABSTRACT

The aim of this study was to predict the physiological consequences of rebreathing carbon monoxide (CO) from a space suit during an extravehicular activity (EVA). A mathematical model of CO dynamics in the human body, based on Bruce and Bruce (2003), was used after appropriate alterations were made to parameter values to reflect changes observed during longer sojourns in microgravity. Simulations predict that rebreathing from the space suit volume during an EVA will result in the accumulation of CO in this volume and an increase of carboxyhemoglobin (%COHb) of the astronaut, from an initial level of 0.5 - 1.0% before the EVA to 1.5 - 2.0% at the end of an EVA lasting for 8 hours. These levels of %COHb have not been associated with serious health effects in normal subjects in earth gravity (1G). The predicted effects of errors in important parameter values of the model, other than the rate of endogenous CO production ( $\dot{V}_{CO}$ ), are minor; however, the predicted rise in %COHb during an EVA increases proportionately with an increase of  $\dot{V}_{CO}$ . Intersubject variability of parameter values combined with an increase of EVA duration could lead to %COHb greater than 2.5%, a level that has been associated with small effects on cognitive abilities.

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## **OBJECTIVES AND RATIONALE**

The aim of this study is to predict the physiological consequences of rebreathing carbon monoxide (CO) from a space suit during an EVA. Astronauts are at some risk of CO poisoning due to: (i) CO contamination of the space suit oxygen supply (up to 1.0 ppm allowed per NASA SSP 30573 Revision F), and; (ii) metabolically-produced CO exhaled by the astronaut during limited exposure to the semi-closed life support system of the space suit. Outputs from a mathematical model will provide indications of CO kinetics with hemoglobin (Hb) and myoglobin (Mb). Widely available clinical information about CO poisoning will provide the basis for interpreting these results with regard to the health and safety of astronauts (Amdur, 1986). Morbidity and mortality resulting from CO exposure are related to %COHb (i. e., the per cent of oxygen binding sites on Hb occupied by CO). Thus, at normal levels of arterial oxygen partial pressure under conditions of 1G and 760 Torr ambient pressure, CO exposure is potentially lethal if more than 60% of Hb binding sites for oxygen are occupied by CO. Headache and possible impairment of brain function ensue at much lower levels of %COHb - e. g., 20-25%. On the other hand, smokers often experience %COHb levels of 6% or more without acute effects.

Although it is easy to estimate CO accumulation in the space suit volume over time, such a simple approach is inadequate to predict CO accumulation in the body because it does not account for the binding of CO to hemoglobin and myoglobin. Furthermore, attempts to extrapolate from the CFK equation (Coburn, et al., 1965) will overestimate risk because this equation applies to CO exposures at a constant level lasting for several hours. Therefore, a more complete model of CO dynamics in the human body is required (Bruce and Bruce, 2003).

## **MODEL DEVELOPMENT AND PARAMETER VALUES**

The base model used for this project is our original model for CO uptake and internal distribution (Bruce and Bruce, 2003), which is a lumped parameter model that contains compartments for muscle and non-muscle tissues, lungs, and vascular volumes (i. e., arterial and mixed venous volumes, and pulmonary and tissue capillary beds). This model was expanded subsequently by separating the muscle compartment into 2 subcompartments (Bruce, et al., 2008). This separation permits the following interpretation of the subcompartments: subcompartment 1 represents the regions of muscle tissues that are served (with respect to gas exchange) by arterioles, capillaries, and venules; subcompartment 2 is served only by capillaries. This model has been validated against muscle  $pO_2$  data in 1G (Bruce, et al., 2008; Bruce, 2010) but has not been tested for microgravity conditions. Other than changes in parameter values, it is expected that our model would apply to the latter case. When whole body metabolic rate of oxygen consumption ( $MRO_2wb$ ) was to be varied during a simulation, a second model (Bruce, et al., 2011) was used because this model also incorporates the typical cardiorespiratory responses to time-varying exercise. Previously we have ensured that the two models produce the same results when  $MRO_2wb$  is constant. See Table 1 for definitions of symbols used in the models.

TABLE 1 - SYMBOL DEFINITIONS

%COHb	Arterial carboxyhemoglobin level as a percentage of the maximum CO binding capacity of Hb
%COMb2	Carboxymyoglobin level in capillary-perfused muscle as a percentage of maximum binding capacity of Mb
Qdot	Cardiac output (ml/min)
Qdotm	Blood flow into muscle compartment (ml/min)
MRO <sub>2</sub> wb	Whole-body metabolic rate of oxygen consumption (mlO <sub>2</sub> /min)
MRO <sub>2</sub> m	Muscle metabolic rate of oxygen consumption (mlO <sub>2</sub> /min)
ParO <sub>2</sub>	Arterial partial pressure of oxygen (Torr)
PB	Environmental pressure (Torr, or psia)
PmxO <sub>2</sub>	Mixed venous partial pressure of oxygen (Torr)
Ptm2O <sub>2</sub>	Average partial pressure of oxygen (Torr) in capillary-perfused compartment of muscle
PrbCO	Partial pressure of CO (Torr) in the rebreathing volume of a space suit
Vb	Total blood volume (ml)
VdotA	Alveolar ventilation (ml/min, at 37°C, 760 Torr, saturated)
VdotCO	Endogenous rate of CO production (ml/min, STPD)
Vsuit	Space suit volume in which CO accumulates

A few changes were made to both models for this project. First, a separate “rebreathing volume” was added to represent the space suit volume from which the astronaut breathes during an EVA. This compartment exchanges gases with the alveolar compartment of the subject by way of ventilation and has an inflowing gas from an external source as well as a possible leak to the environment. Second, alterations of physiological parameters due to a sojourn in microgravity were encoded in the models, as discussed below.

Parameter values for the models were chosen to represent healthy male subjects. The first subject studied (S120) is a subject from our previous publications; we had acquired values for several important cardiorespiratory parameters for him from collaborators (e. g., Benignus, et al., 1994). The second subject (referred to as “Norsk”) is a composite based on astronauts studied by Norsk, et al. (2015). S120 was 24 years old and Norsk was 49. See Table 2 for other basic parameters.

TABLE 2 - PHYSIOLOGICAL PARAMETERS OF SUBJECTS (AT 1 G)

Subject	Age (yr)	Height (m)	Weight (kg) @1G	[Hb] gm/ml @1G	Resting cardiac output (ml/min) @1G	Blood volume (ml/kg) @1G
S120	24	1.79	72.7	0.145	5800	60.94
Norsk	49	1.79	82	0.145	6200	60.94

It was assumed that an EVA would not take place until adaptation to the space environment had occurred; thus, we used parameter values reported after 90 or more days in microgravity. Specifically, it was assumed that Hb content decreased by 10% (Alfrey, et al., 1996; Cogoli, 1981; Smith, et al., 2001, 2005), total blood volume decreased by 17% (Johnson, et al., 1977; Udden, et al., 1995), and cardiac output increased by 35% (Norsk, 2015). It was assumed that astronauts are more physically fit than average, and that their muscle mass is 10% greater than typical for their body weight; however, we also assumed a 20% loss of muscle mass during a sojourn in microgravity (Bagley, et al., 2012). Although this assumption may be somewhat high, the resulting concentration of Mb is more critical and is unknown. Finally, because measurements of ventilation in microgravity were unavailable to us, we chose values for alveolar ventilation that resulted in an arterial pO<sub>2</sub> of 100-120 Torr when breathing 100% O<sub>2</sub> at 4.3 psia (i. e., 222 Torr), assuming an MRO<sub>2wb</sub> that was 50% higher than a typical resting level of 220 ml/min (STPD). Although the level of ventilation has little effect on rebreathing from the space suit volume, it does determine the level of %COHb at the onset of rebreathing. In the model, when MRO<sub>2wb</sub> changes, alveolar ventilation and cardiac output are changed in the same direction and proportion.

Endogenous CO production rate (VdotCO) deserves special consideration because it is the most influential unknown parameter of the model. Endogenous CO production results primarily from the degradation of heme. We initially assumed that endogenous CO production was somewhat lower in microgravity than at 1G based on reports that red blood cell mass (RBCM) levels post-flight were as much as 17% lower than pre-flight values (Alfrey et al., 1996; Udden et al. 1995). However, the time course over which this decrease in RBCM occurs is not clear from the published data. Alfrey et al. (1996) suggest that “the decrease in newly produced RBCs occurs within the first day of flight” whereas Udden et al. (1995) reports that RBC destruction occurs at the rate of ~1%/day - a nearly-normal rate. In addition, the variable responses of the 3 subjects studied in the Alfrey and Udden papers make it difficult to predict endogenous CO production with any degree of confidence.

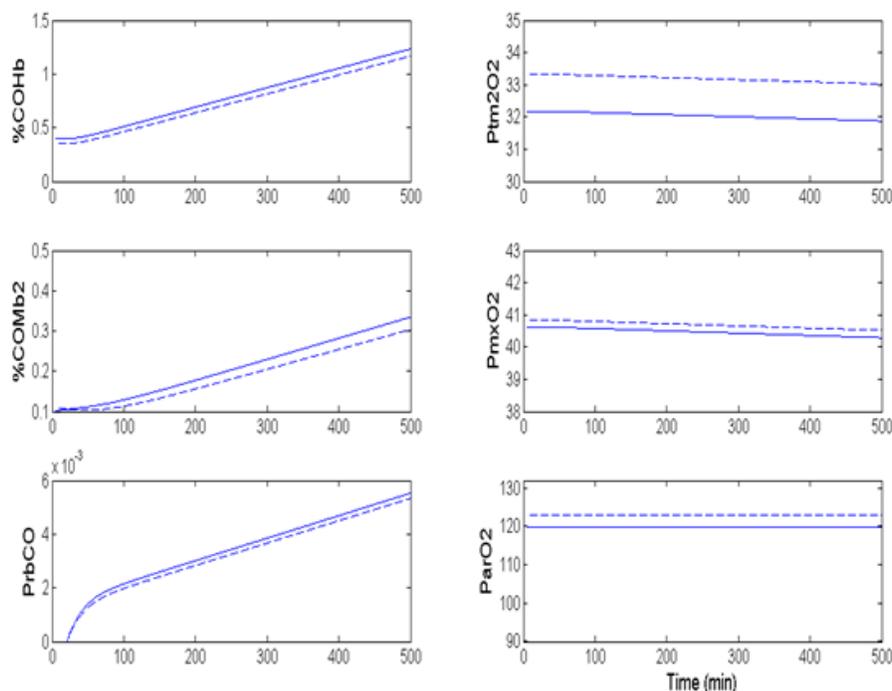
Also unclear is the mechanism responsible for the decrease in RBCM. This decrease occurs despite “nearly normal rates of red cell production in bone marrow as measured by erythron-iron turnover” (Udden, 1995), suggesting that the early stages of erythropoiesis are not affected by microgravity. However, the 31% decrease in erythropoietin (Udden, 1995) would be expected to decrease the viability of RBCs in the Proerythroblast and Erythroblast stages (both of which contain heme), which would be consistent with the observed decrease in RBCM in spite of “nearly normal” Fe uptake by immature RBCs. Therefore, to err on the side of safety, all simulations (unless noted otherwise) assumed that VdotCO was 50-100% greater than normal. “Normal” VdotCO was calculated from body weight as reported in Table 1 of Coburn and Forman (1987); for a 70 kg male, normal VdotCO is ~20 micromoles/hour or 0.007 ml/min. In simulations that follow, VdotCO ranges from 0.011 to 0.016 ml/min (Table 3).

## **SIMULATION RESULTS**

### **1. Baseline simulations**

Our “baseline” simulation represents a situation of rebreathing from a space suit volume of 42.0 L. for 8 hours at 222 Torr. The suit initially contains 100% O<sub>2</sub>. The starting values (i. e.,

the initial conditions) for %COHb and %COMb2 for a given subject were determined by first simulating unconstrained breathing (at the specified  $\text{MRO}_2\text{wb}$  on 100%  $\text{O}_2$  at 222 Torr ambient pressure for 8 hours without rebreathing to determine the steady-state values of %COHb and %COMb2. **NOTE:** The initial 20 minutes of the simulations that follow represent unconstrained breathing to the environment without rebreathing; these results confirm that, before any rebreathing occurs, the simulation begins at the initial conditions found above for %COHb and %COMb2. The baseline simulations for the young and middle-aged subjects are shown in Figure 1. For these simulations  $\text{VdotCO}$  was 50% greater than the calculated “normal” value for body weight. Rebreathing from the space suit volume begins at  $t = 20$  min (evident particularly in the graph of  $\text{PrbCO}$ ). Thereafter, CO content of both blood and muscle tissues increases steadily with time.



**Figure 1 - Baseline simulations for 2 different male subjects (Solid: Norsk; dashed: S120). Eight hours of rebreathing from a space suit volume of 42.0 L.  $\text{VdotCO}$  is 50% above calculated normal for each subject. See Table 3 for other parameters.**

Initially, both subjects have a low level of COHb ( $<0.5\%$ ) during unconstrained breathing preceding rebreathing from the suit volume. The older subject (Norsk) has somewhat higher levels of %COHb and %COMb2, but the differences are minor. For both simulations, 75% or more of the CO released through endogenous production ends up bound to Hb or Mb. Deep muscle ( $\text{PtmO}_2$ ) and mixed venous ( $\text{PmxO}_2$ ) oxygen pressures are consistent with those we calculated previously for normoxic subjects in 1 G (Bruce, et al., 2008). Both partial pressures exhibit physiologically insignificant decreases as CO content of the body increases. Neither simulation suggests that any negative effects would ensue from accumulation of CO during an 8-hr EVA. To assure an abundance of caution, however, for the remaining studies  $\text{VdotCO}$  was assumed to be twice the calculated “normal” value.

## 2. Effects of changing VdotCO, Hb mass, and blood volume

VdotCO, Hb mass, and blood volume are critical parameters for determining how much CO accumulates in the body during the 8-hr EVA. To assess the effects of changing our assumed values for these parameters, multiple simulations were run while varying one of the three parameters and holding the other two at their nominal levels (indicated by open squares in the graphs). Results are shown in Figure 2.

The change in %COHb over 8 hours is directly proportional to VdotCO and inversely proportional to Hb concentration and blood volume. VdotCO has the largest effect. Even though the initial value of %COHb also is higher when VdotCO is increased, the final value (at 8 hours) never exceeded 2.0% in these simulations. The initial value of %COHb also is higher when VdotCO is increased, the final value (at 8 hours) never exceeded 2.0% in these simulations.

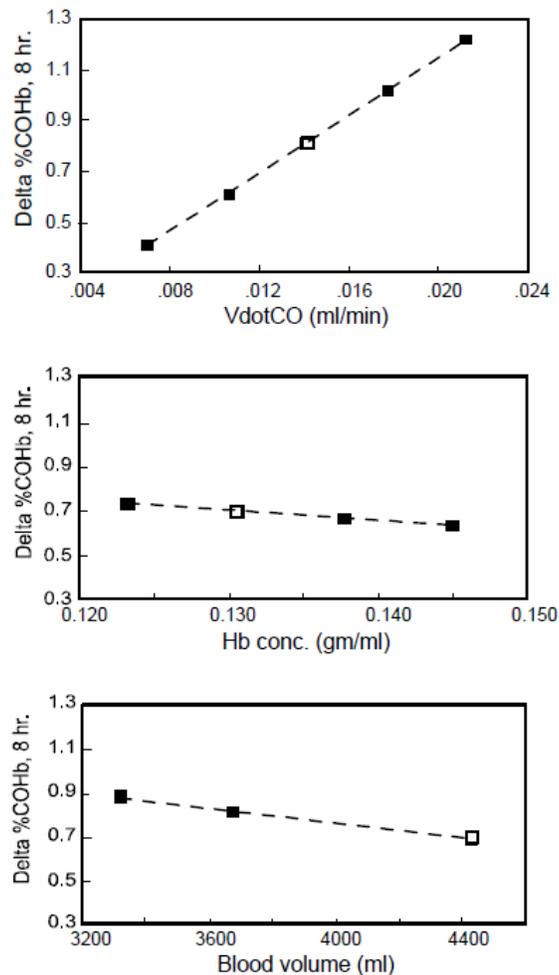
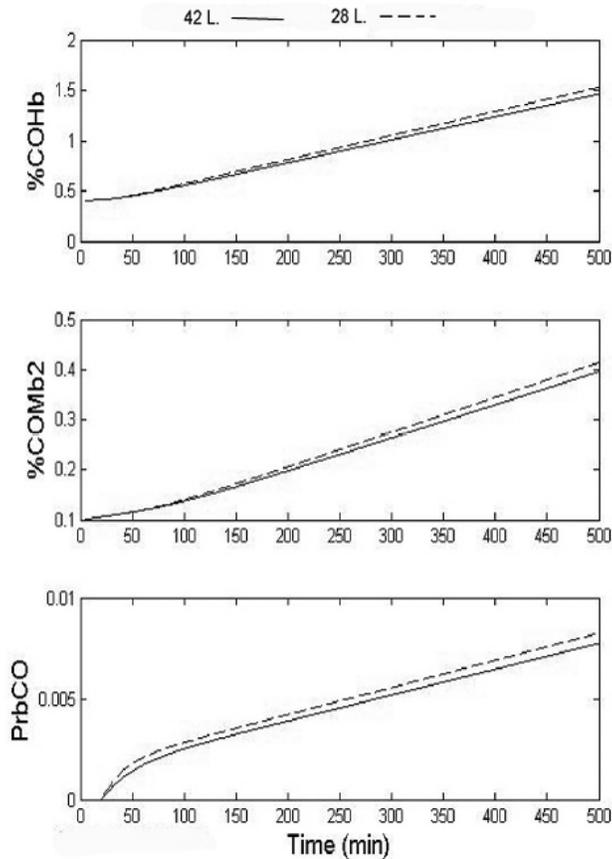


Figure 2 - Sensitivity of change in %COHb after 8 hr of rebreathing to: (top) VdotCO; (middle) Hb concentration; (bottom) total blood volume. Data from S120. Open symbols represent “nominal” values that were held constant when the 2 other parameters were varied. See Table 3 for other parameters.

### 3. Effects of suit volume

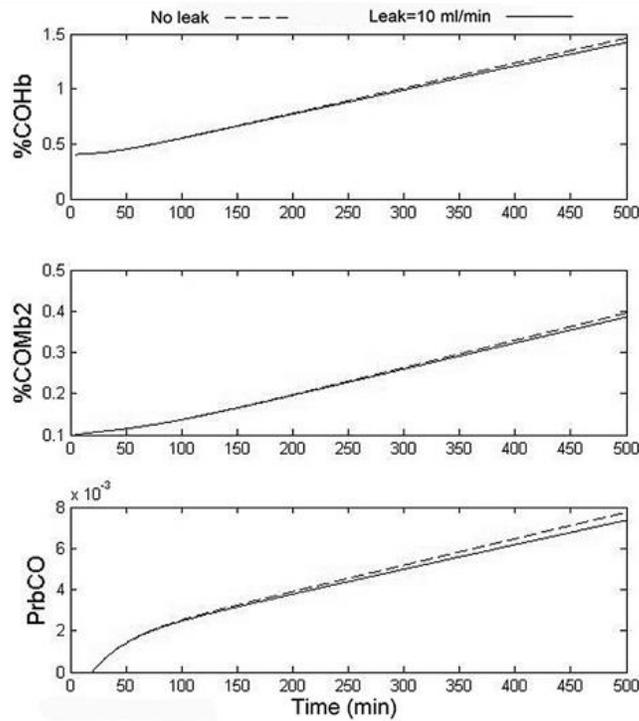
Suit volume influences the rate of build-up of CO concentration in the volume from which rebreathing occurs. This influence has minor effects, as seen in Figure 3 when suit volume ( $V_{\text{suit}}$ ) was reduced from 42 to 28 L, because most of endogenously produced CO is bound to Hb and Mb.



**Figure 3 - Effect of decreasing the suit volume on CO accumulation during an 8-hr EVA. Solid:  $V_{\text{suit}}=42$  L. Dashed:  $V_{\text{suit}}=28$  L. Subject Norsk. For other parameters see Table 3.**

#### 4. Effects of a leak

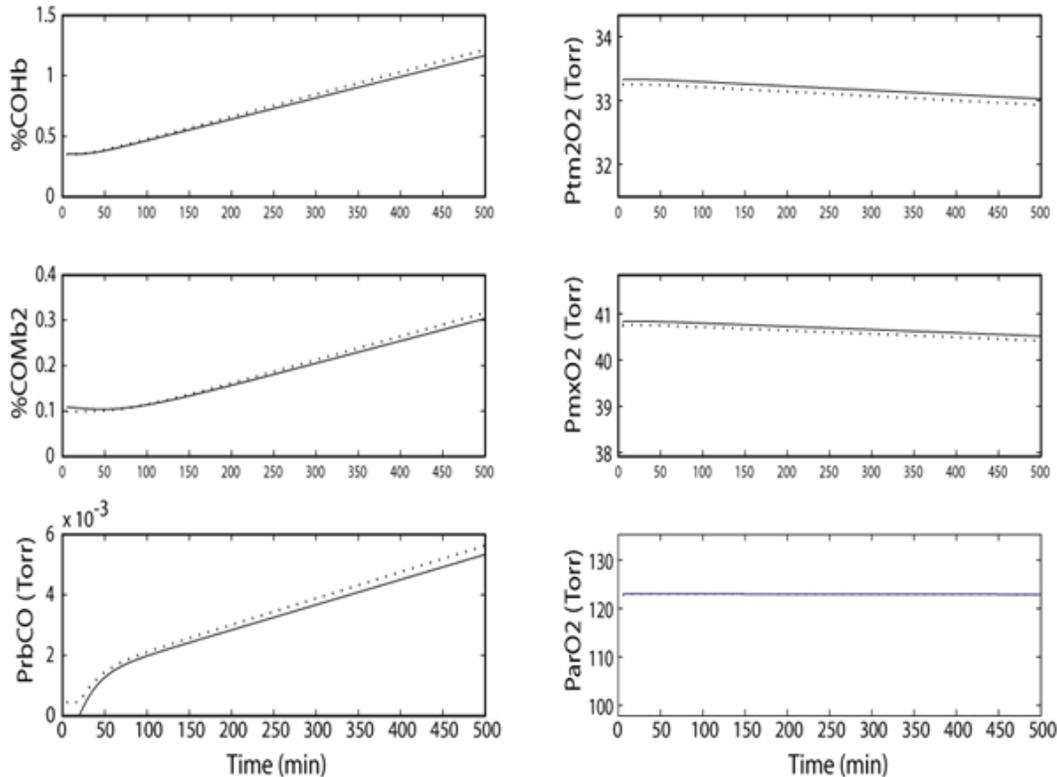
Another concern is the occurrence of a leak from the space suit. We conducted a simulation of a leak of 34.2 ml/min (equal to 10 ml per min at 14.7 psia and 21.1°C) and compared the results to those with no leak (Figure 4). The leak removes some CO from the suit volume but the effect on %COHb is minor. There is a negligible effect on oxygen partial pressures (not shown).



**Figure 4 - Effect of a small leak in the space suit. Dashed: No leak. Solid: Leak=34.2 ml/min (equivalent to 10 ml/min at 21.1°C, 760 Torr) Subject Norsk.**

## 5. Contamination of the oxygen supply

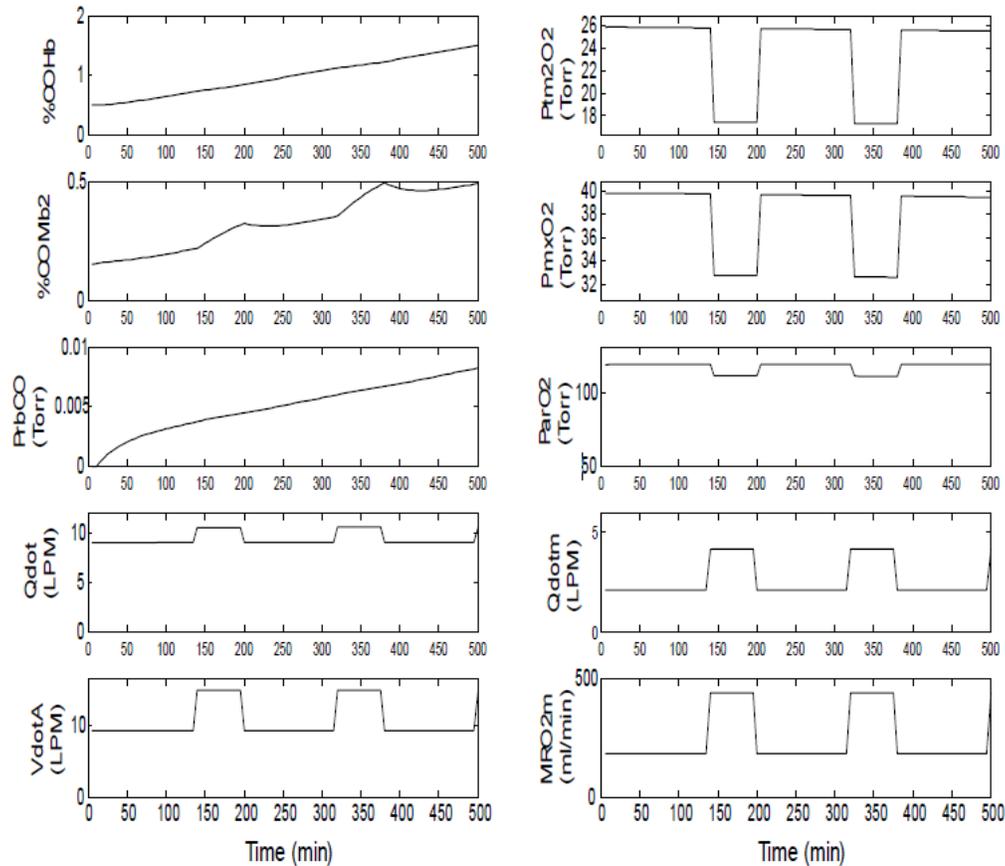
The oxygen supply is allowed to have up to 1 ppm of CO contamination. To estimate an upper limit to the effect of this contamination, a simulation was run with 2 ppm CO in the oxygen supply. This contamination produces small increases in %COHb and %COMb2 and very small decreases in oxygen partial pressures (Figure 5).



**Figure 5 - Effect of adding 2 ppm CO to the oxygen supply. (Subject S120). Solid: no CO in oxygen supply. Dotted: 2 ppm CO in supply. See Table 3 for other parameters. Effect on P<sub>a</sub>rO<sub>2</sub> is too small to be seen at this scale.**

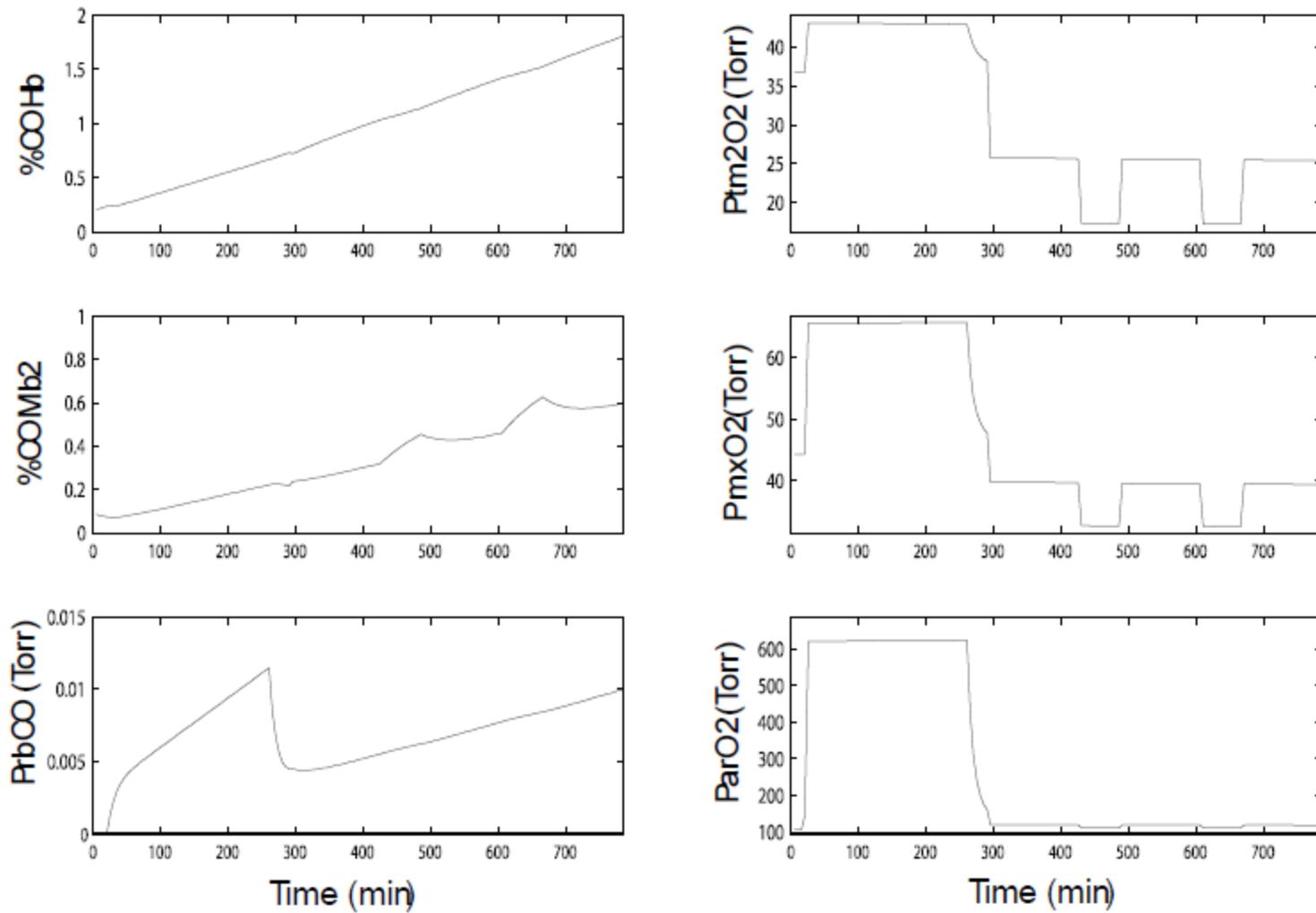
## 6. Time-varying energy expenditure during the EVA

The previous simulations assumed that energy expenditure, as measured by MRO<sub>2</sub>wb, was constant throughout the EVA, at a level about 50% greater than resting. It is expected that MRO<sub>2</sub>wb will increase episodically during an EVA. Therefore, a simulation was run in which there are two one-hour episodes in which MRO<sub>2</sub>wb is increased from 50% above resting to nearly three times resting (i. e., “exercise”) as a result of increasing the muscle metabolic rate (MRO<sub>2</sub>m). Figure 6 shows that the increase in muscle blood flow during “exercise” carries more CO into muscle tissues and significantly increases the amount of CO bound to Mb. As expected, the increase in ventilation during exercise maintains P<sub>a</sub>rO<sub>2</sub> nearly constant but the corresponding increases in cardiac output (Q<sub>dot</sub>) and muscle blood flow (Q<sub>dot</sub>m) do not prevent falls in muscle tissue and mixed venous oxygen pressures.



**Figure 6 - Simulation of EVA during which there are two episodes of elevated MRO<sub>2wb</sub> (140<t<200 and 320<t<380). Base MRO<sub>2wb</sub>=422 ml/min; elevated MRO<sub>2wb</sub>=678 ml/min. Subject Norsk. For other parameters see Table 3.**

Finally, the entire process of preparation followed by an EVA was simulated. First, the subject starts at rest (MRO<sub>2wb</sub>~280 ml/min) on normoxic air at PB=14.7 psia. Then 4 hours of prebreathing 100% O<sub>2</sub> at this pressure follows. Next, over the course of 30 min PB is lowered from 14.7 to 4.3 psia. This is followed by an EVA in which the basic MRO<sub>2wb</sub> is ~150% of resting (MR O<sub>2wb</sub>~400 ml/min), and during which there are two one-hour episodes of elevated MRO<sub>2wb</sub> (~700 ml/min). Results are presented in Figure 7. It is apparent that at the end of the prebreathe and decompression periods, there is CO in the suit and %COHb is already elevated. Consequently, during the EVA %COHb increases to a higher level than in previous simulations; however, the final (highest) predicted value is somewhat less than 2%. These results may be compared with Figure 6, which simulate a similar EVA for this same subject without the prebreathe period. Note that the initial values for %COHb and %COMb2 (i. e., for t<20 min) are lower in Figure 7 because the inspired pO<sub>2</sub> is much higher than for Figure 6; thus, more Hb is bound to oxygen.



**Figure 7 - Simulation of prebreathing 100% O<sub>2</sub> in suit at resting MRO<sub>2wb</sub> (279 ml/min), followed by decompression to 4.3 psia, then 8 hours of EVA at somewhat elevated MRO<sub>2wb</sub> (422 ml/min) with two periods of more intense exercise (678 ml/min). Subject Norsk. See Table 3 for other parameters.**

## DISCUSSION

Endogenous CO production ( $\dot{V}_{CO}$ ) results in an elevation of %COHb after 8 hrs of rebreathing from the space suit during an EVA. In all of the simulations conducted to date, Hb absorbs most (70-85%) of the CO produced endogenously. An additional 5-10% is absorbed by Mb. Because the level of  $\dot{V}_{CO}$  in microgravity was not available and the degree of red cell hemolysis probably varies with time in microgravity, we assumed a value for  $\dot{V}_{CO}$  greater than at 1G (adjusted for body weight), usually 1.5 to 2.0 times that calculated from published measurements (Coburn and Forman, 1987). The amount of increase of %COHb varies directly with the assumed  $\dot{V}_{CO}$  (Figure 2) but to reach clinically significant %COHb during an 8-hr EVA would require an even larger  $\dot{V}_{CO}$  than we assumed. Such a large value seems unlikely but cannot be excluded without measurements of exhaled CO in microgravity. Suit volume, leak from the suit, and 1-2 ppm CO contamination of the oxygen supply have minor effects on %COHb during an EVA.

The amount of endogenously produced CO bound to Hb after an 8-hr EVA is small enough that oxygen transport by Hb is not impaired significantly. It should be noted, however, that periods of elevated  $\dot{M}R_{O_2wb}$  (achieved by increasing  $\dot{M}R_{O_2m}$  of muscle tissues) cause an increase of %COMb2 due to increased transport of CO to muscle via elevated muscle blood flow. Consequently, the time needed for removal of excess CO from the body post-EVA would be lengthened (Bruce and Bruce, 2005). Concomitantly, oxygen partial pressure in muscles (e.g.,  $P_{tm}O_2$ , Figure 6) is predicted to fall even when arterial  $pO_2$  does not. Muscle subcompartment 2 is envisioned in the model as representing deep muscle tissues that undergo gas exchange with capillaries but not with arterioles and venules (Bruce, et al., 2008). Predicted  $P_{tm}O_2$  from this model has been compared with experimental measurements of  $pO_2$  in deep muscle tissues taken during normoxia and hypoxic hypoxia (Bruce, et al., 2008; Bruce, 2010). It generally lies in the middle of the lower half of the distribution of actual  $pO_2$  readings under those circumstances. Thus, one can expect localized regions of deep muscle to have lower  $pO_2$ s during the EVA than the predicted  $P_{tm}O_2$ . Preliminary studies have predicted that brain tissue  $pO_2$  levels fall less than  $P_{tm}O_2$  falls during hypoxic hypoxia (Bruce, 2010). Thus, it seems unlikely that these pressures would be low enough to cause localized hypoxic injury (often attributed to  $pO_2$  less than 5 Torr) in muscle or brain tissues. It must be noted, however, that the models have not been validated for predicting tissue  $pO_2$ s in microgravity. On the other hand, excepting changes in parameter values (some of which were incorporated), it is expected that these models would apply to the latter case. Also, alveolar ventilation may be erroneous because its value was chosen on the basis of predicted arterial  $pO_2$ , not on the basis of measured data.

When the entire sequence of EVA prebreathing, decompression, then EVA was simulated (Figure 7), it was predicted that prebreathing on normobaric oxygen results in some accumulation of CO in the suit and the body, which causes %COHb to rise to a higher level during the EVA than would otherwise occur. Nevertheless, peak %COHb was still well below a level expected to cause disability due to impaired oxygen delivery. On the other hand, small effects on cognitive function have been reported in non-smokers at %COHb levels as low as 2.5% (Amdur, 1986). Although predicted %COHb does not reach this level, it is clear that some combinations of the factors described in Figure 2, plus possible contamination of the oxygen supply, could raise %COHb to 2.5% or more. In particular, any further increase of %COHb due to lengthening the duration of an EVA should raise concerns about the potential for cognitive

impairment. Furthermore, it should be remembered that the initial level of %COHb varies across subjects and ranges from near 0% to nearly 2% in non-smokers (Benignus, et al., 1994).

Because our highest predicted %COHb approaches 2%, it would be appropriate to validate the assumed value for  $\dot{V}_{CO}$  through actual measurements in microgravity. To further validate the predictions from this modeling study, the concentration of exhaled CO could be measured during normobaric, normoxic conditions in microgravity to put an upper limit on  $\dot{V}_{CO}$  - the most influential unknown parameter in the model. With the simultaneous measurement of ventilation, the exhaled CO data could be used in our model to estimate  $\dot{V}_{CO}$ . Alternatively, collection of exhaled gas for 20-30 min could provide necessary data for estimating  $\dot{V}_{CO}$ ; both the mean CO concentration in the collection bag and the total volume of this bag would be needed in addition to the exact collection time.

## CONCLUSIONS

1. It is likely that CO accumulation in the space suit due to its endogenous production is insufficient to present a potential threat to health and safety during an 8-hour EVA.
2. Any further increase of %COHb beyond that predicted here - e.g., due to lengthening the duration of an EVA - should raise concerns about the potential for cognitive impairment.
3. Validation of the value of  $\dot{V}_{CO}$  in microgravity would strengthen considerably the findings of this modeling study.

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## APPENDIX

TABLE 3. PARAMETER VALUES FOR THE FIGURES

Subject	MRO2wb MI*/min	MRO2m MI */min	Qdot ml/min	Vb/kg ml/kg	Vsuit L (BTPD)	VdotCO MI (STPD)/min	VdotA ml#/min
S120	436	208	10298	50.58	42	0.011	9230
Norsk	492	242	11639	50.58	42	0.013	9230
S120	436	208	Varies	Varies	42	Varies	9230
Norsk	492	242	11639	50.58	42	0.016	9230
Norsk	492	242	11639	50.58	28	0.016	9230
Norsk	492	242	11639	50.58	42	0.016	9230
Norsk	492	242	11639	50.58	42	0.016	9230
S120	436	208	10298	50.58	42	0.014	9230
S120	436	208	10298	50.58	42	0.014	9230
Norsk	422	183	9059	50.58	42	0.016	9243
Norsk	678	439	10592	50.58	42	0.016	14854
Norsk	279	101	8210	50.58	42	0.016	5600
Norsk	422	183	9135	50.58	42	0.016	9244
Norsk	678	439	10648	50.58	42	0.016	14854

\* 37°C, 760 Torr, dry

# 37°C, 760 Torr, saturated

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