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Disappearance of carbon monoxide from the blood

Comparison of the one-exponential and two-exponential elimination models for rat

by Kari Kurppa, MD¹

KURPPA K. Disappearance of carbon monoxide from the blood: Comparison of the one-exponential and two-exponential elimination models for rat. *Scand j work environ health* 7 (1981) 233—236. The elimination of carbon monoxide from rat blood was studied from a starting point of a nonsteady-state concentration of 40 % for carboxyhemoglobin (COHb). The accuracy of the fit was statistically improved by the employment of a two-exponential elimination model rather than that of the one-exponential model. Yet, the differences in the COHb estimates attained with the two models were negligible. Therefore, for practical purposes, the one-exponential model seems reasonably reliable for estimating COHb.

Key terms: carboxyhemoglobin.

Most earlier studies have concluded that carbon monoxide (CO) is eliminated at a constant exponential rate. This conclusion means that there is a stable half-time for carboxyhemoglobin (COHb) (1, 4, 5, 9, 10, 13). The half-time concept is convenient for practical purposes. However, a biphasic decline in the concentration of COHb has recently been reported after nonsteady-state exposure conditions (3, 8, 14). An initial rapid disappearance of COHb followed by a slower CO elimination seems possible. This observation is interesting since it may have practical importance in the calculation of the postexposure body burdens of CO. It might challenge the applicability of the current practice of using a single COHb half-time for estimation purposes. Therefore, it was of interest to study the extent to which

the estimates of COHb by the one-exponential and two-exponential elimination models actually deviate from each other.

Animals and methods

Nineteen male Wistar rats (294 ± 29 g, mean $\pm$ SD) were exposed to 1,000 ppm of CO for 22 min. The steady-state COHb concentration is approximately 60 % at this exposure level, and it is reached in about 1.5 h (7, 11). The exposure took place in a dynamic exposure chamber of 1 m³ equipped with an infrared analyzer for the measurement and control of CO concentration (Miran 1A, Wilks Scientific Corp). The rats were decapitated and bled into heparinized glass tubes.

The concentrations of COHb were determined by gas chromatography (2). The coefficient of variation was about 3 % (rel) at the COHb level of 30 % (nine determinations). The mean endogenous COHb of the rats (0.4 ± 0.1 %, mean $\pm$ SD) was calculated from the blood samples of 15 nonexposed animals.

Parameter values for the CO elimination

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models were optimized by the Marquardt's nonlinear least squares iteration method (6, 12). A Tektronix 4052 minicomputer was used for the calculations. In order to ensure the best solutions, several starting values were tried for the parameters.

The average endogenous COHb concentration of 0.4 % was inserted in the models

Fig 1. The carboxyhemoglobin (COHb) elimination curves of the one-exponential (broken line) and two-exponential (solid line) elimination models.

as an asymptote. The equation for the one-exponential model followed the formula

$$\text{COHb}_t = (\text{COHb}_0 - 0.4)e^{-bt} + 0.4,$$

where COHb_0 denotes the actually measured concentration of COHb at the beginning of the elimination process and COHb_t the actual concentration of COHb at time t . The two-exponential model was described by the formula

$$\text{COHb}_t = ae^{-bt} + ce^{-dt} + 0.4,$$

where $a + c = \text{COHb}_0 - 0.4$, symbols b and d denoting rate constants.

Fits for the elimination models were first computed from the crude data, ie, all of the COHb results were used. COHb values that deviated more than two standard deviations from the respective estimates simultaneously in both elimination models were deleted from the final analyses. One such data point (9 min, 29.6 % COHb) was found. (The result of the statistical comparison remains essentially similar with or without the deletion of the "outlier.")

Table 1. The optimized parameters of the carboxyhemoglobin (COHb) elimination models by the Marquardt's least squares iteration method.^a

Model	Parameter		SE
One-exponential $y = ae^{-bt} + 0.4$	a [% COHb]	38.6	0.4
	b [min^{-1}]	0.022	0.001
Two-exponential $y = ae^{-bt} + ce^{-dt} + 0.4$	a [% COHb]	13.8	7.5
	b [min^{-1}]	0.05	0.02
	c [% COHb]	25.6	7.6
	d [min^{-1}]	0.016	0.002

^a $y = \text{COHb}_t$ (%), e = base of natural logarithms, t = time in minutes, SE = parameter standard error.

Table 2. Comparison of the accuracy of the one-exponential and two-exponential elimination models by the F test of variances with a one-sided risk level.^a

Model	Sum of squares	df	F	p
One-exponential	12.8	16	—	—
Two-exponential	4.4	14	14.4	< 0.0005

^a df = degrees of freedom; $F = [(12.8 - 4.4)/2]/(4.4/14) = 14.4$.

The mathematical accuracy between the COHb data and the respective estimates by the elimination models was compared by the *F* test of variances.

Results

Table 1 presents the optimized parameters of the elimination models. The two-exponential model showed relatively large parameter errors.

The elimination curves of the one-exponential and the two-exponential models are visualized in fig 1. The curves intercepted twice but did not deviate far from each other. The one-exponential curve was slightly inaccurate at both ends of the COHb data.

The application of the two-exponential model, instead of the one-exponential model, statistically improved the mathematical accuracy of the fit (table 2).

Discussion

The accuracy of the two-exponential model was statistically superior to that of the one-exponential model. Thus, it appears that the elimination process of CO from the blood may be more complex than that described by a one-exponential model (half-time of about 32 min for COHb). This observation is interesting with respect to the theory of the kinetics of CO in the body.

The COHb estimates of the two elimination models studied do not differ much, despite the statistically significant improvement of the accuracy attained with the two-exponential model. The increase in the accuracy of the fit seems negligible for practical purposes. For instance, with a hypothetical COHb value of 40 % as a starting point, the one-exponential model predicts a COHb concentration of 25.9 % after 20 min, while the two-exponential model yields an estimate of 24.2 % at the same time point. After 180 min from the start of the elimination, the COHb estimates of the one-exponential and two-exponential models would be 1.2 and 1.8 %, respectively.

The two-exponential model seems too complex to be prudently fitted with the

present number of observations since the parameter errors become unreasonably large. Obviously, at least a couple of hundred observations would be needed in order to achieve error limits comparable to those of the one-exponential model.

In conclusion, the accuracy of the fit in the simulation of COHb disappearance is statistically improved with the use of the two-exponential model instead of the one-exponential model. The practical significance of this improvement seems negligible, however.

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