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A Noninvasive Method For Rapid Diagnosis Of Carbon Monoxide Poisoning

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Abstract

Purpose: To determine the relationship between exhaled carbon monoxide (CO) and blood percent carboxyhemoglobin (%COHb) in acute CO poisoning and to develop screening protocols to simplify the interpretation of results.
Basic procedure: In this prospective trial, 45 patients were examined following CO exposure. Nineteen were breathing air and 26 were being administered oxygen at the time of the test. A commercial breathalyzer measured exhaled CO. All patients whose breath CO concentrations were > 25 parts per million had venous blood drawn immediately.
Important findings: There was a significant correlation between exhaled CO and venous blood %COHb, but the correlation was affected by breathing oxygen, and the variability in the relationship was greater in the emergency setting than previously reported in laboratory trials.
Conclusion: End-tidal CO can be measured noninvasively in less than one minute in an emergency setting using a portable breathalyzer. The calibration curves developed may be used to estimate the %COHb from the breathalyzer reading for patients breathing air with a 95% confidence interval of * 6.30 %COHb. Cut-off scores for breathalyzer readings of 53 ppm for air breathers and 43 ppm for oxygen breathers provide a quick screening for %COHb of 10% or higher. Overall, the screening procedure correctly identified 23 of the 25 patients whose %COHb was above 10% and had a false negative rate of only 13.3%. Despite the fact that in this set of data the estimation of %COHb was somewhat lacking in precision, the ability to classify was surprisingly good. In this paper, significant, acute CO exposure is defined as having %COHb > 10% and the protocol developed is therefore limited to this definition.

INTRODUCTION

Carbon monoxide (CO) poisoning, accidental or intentional, is the leading cause of death by poisoning in the United States ([1]). The diagnosis is frequently overlooked because of the nonspecific nature of the most common symptoms: fatigue, headache, weakness, dizziness, confusion, or transient loss of consciousness ([2,3]). Patients arriving at an acute care facility with these symptoms have no specific clinical findings to suggest CO poisoning, although the nature of the incident may clearly suggest the possibility of CO exposure. If a high index of suspicion is present, blood is then drawn and the percent carboxyhemoglobin (%COHb) is measured in the laboratory utilizing a CO-oximeter. Blood carboxyhemoglobin begins to decrease after removal from the source of CO, but significant amounts of CO may be attached to intracellular moieties and thus be undetectable with current laboratory technology. As a result, patients can have serious CO poisoning with low carboxyhemoglobin values, particularly if there are long delays to blood sampling.

Carbon monoxide is eliminated from the body as a gas in exhaled air. Measuring exhaled CO is feasible, and relating exhaled CO to the %COHb has been done in the laboratory ([4,5,6]). Stewart et al. estimated venous %COHb by measuring the CO (in parts per million, ppm) of the exhaled breath in 56 firemen in a laboratory setting using an Ecolyzer model 2100 (3). Although breath samples were validated by gas chromatography (error ± 1.2 ppm), the breath CO was plotted against a theoretical blood COHb, not against observed data. The authors reported that the 95% confidence interval for estimating COHb percent concentration was a very precise ± 0.5 %COHb, but the precision of the relationship between breath and the observed blood CO has never been established in an emergency setting. Hand-held devices for measuring exhaled CO via breath analysis are available and are commonly used in smoking cessation programs to detect low concentrations of CO. According to Jarvis et al. ([7]), the alveolar CO levels in 75 smokers tested

with an Ecolyzer EC50 correlated with blood COHb. However, as expected, the data concentrated at the low end of the COHb range (COHb 7%). The Jarvis study was done in a laboratory and used the second sample of alveolar air because it had a higher CO concentration. The Jarvis equation had the same slope as the Stewart equation but a different intercept, perhaps attributable to instrument calibration. The 95% confidence interval was about ± 1.6 %COHb, three times wider than the Stewart result. In both the Stewart and Jarvis studies, patients were breathing air during the test. Normally, oxygen is administered to anyone suspected of having CO poisoning. It is not known if the Stewart curve calibrated in air is appropriate for patients breathing oxygen.

Our objectives were to determine the relationship between exhaled CO and blood %COHb in acute CO poisoning and to assess the value of the breathalyzer in an emergency setting in which the patient may be breathing either air or oxygen.

MATERIALS AND METHODS

The study protocol was approved by the University of Texas Committee for the Protection of Human Subjects. Because breathalyzer evaluation is noninvasive and all blood tests were medically necessary, written informed consent was not required by our institutional review board. Ten technicians in the emergency medicine center were trained in the use of the Bedfont EC50Toxco portable breathalyzer (Bedfont Scientific, Ltd., Kent, UK), thus sampling technique may have varied slightly. Patients whose circumstances or symptoms suggested CO exposure were verbally instructed in the purpose of the breathalyzer. After the ready light indicated that sampling could begin, patients were asked to hold their breath for 15 seconds and then exhale into the mouthpiece. All patients whose exhaled CO concentrations were 25 ppm (which according to the Stewart curve should correlate with a blood COHb of greater than 6%) had venous blood drawn immediately. While heavy smokers may achieve a blood COHb of 6% or greater, utilizing this value made it unlikely that patients with significant environmental CO exposure would be overlooked. Blood samples were collected in standard purple-stoppered tubes containing ethylenediaminotetraacetate (EDTA) for anticoagulation and were analyzed using a CO-oximeter (Instrumentation Laboratories, Lexington, MA). The interval between breath sampling and blood testing was never more than 10 minutes and the average time to blood sampling was three minutes. Blood and breath samples were not drawn simultaneously because only patients whose breathalyzer results suggested CO exposure had a clinical indication for blood CO measurement. The method of delivery of supplemental oxygen, if any, was recorded.

Data collected from three patients who experienced difficulty holding their breath for 15 seconds due to dyspnea were excluded from this study because they violated the requirements of the test protocol and are not counted in the 45 patients referenced earlier.

STATISTICAL ANALYSIS

The relationship between alveolar CO and venous blood %COHb in this series of patients was analyzed and compared with the Stewart curve. Simple and multiple regression analyses were used to fit lines through the data collected. Statistical tests were: Student's t-tests on individual coefficients, Fisher's F test on the multiple regression models, or chi-square tests on contingency tables. Significance levels were all < 0.01 except for the oxygen effect, which had a p-value of 0.025 in a sequential F-test. The SPSS statistical software was used to make these computations.

RESULTS

The study population consisted of 45 patients who had complete data entries. Sources of CO included house fires, malfunctioning home heating appliances, intentional automobile exhaust, and accidental environmental exposure to forklift exhaust. When examined, all patients were breathing spontaneously. Symptoms at presentation included headache, dizziness, transient loss of consciousness, palpatations, and subjective shortness of breath. Twenty-six patients had received oxygen either via nasal cannula or by non-rebreather face mask before testing. One severely poisoned patient, defined by transient loss of consciousness, was treated with hyperbaric oxygen therapy. All other patients were treated with 100% sea level oxygen via non-rebreather face mask for periods ranging from 2.5 to 4 hours, until symptom resolution.

THE STEWART CURVE

To evaluate the usefulness of the previously published Stewart calibration curve, we recast it in a more standard form (regression) in which the response variable (%COHb) is on the vertical axis and the predictor variable (breath CO in ppm) is on the horizontal axis. The curve is parabolic, but the equation can be approximated by the linear portion for values of breath CO below 200 ppm.

THE DATA AND MEASUREMENT PRECISION

Alveolar CO concentrations by breathalyzer (first sample) and venous COHb values are shown in Table 1 for two classes of patients: those breathing air and those who received oxygen in transit. Six duplicate breath samples were taken among air breathers and are noted in Table 1. The correspondence between these readings was good. The two duplicates taken from patients breathing oxygen through a face mask differed by more than 40 ppm. It is not known why the two oxygen duplicates varied so much. In order to have consistent data, when duplicate samples were taken, the first of the two samples was used (rather than the mean). The only exception was one of the extreme duplicate pairs (5,56) in which the second reading of 56 was consistent with the %COHb, and the first reading was an outlier. An outlier was defined as being more than four standard deviations from the regression line. It is recorded as (56,5) in Table 1 so it will be sorted in the order of the reading used. Two observations in the oxygen data were positioned to have a strong leverage influence on the oxygen curve (based upon statistical leverage statistics). Both were deleted in the calibration process to avoid biasing the models. They were reinstated in the analysis of the performance of the cut-off scores.

Figure 1

Table 1: Patient Population: Breathalyzer and Carboxyhemoglobin Values

Breathing air before breathalyzer (ppm)*	Blood carboxy-hemoglobin (% COHb)	Breathing O_2 in transit before breathalyzer (ppm)*	Blood carboxy-hemoglobin after O_2 (% COHb)
14 (15)	3.2	25	5.4
27	7.5	25	2.0
32	9.3	33	8.3
34 (40)	10.2 (9.7)	36	10.0
38	11.9	36	6.1
38	6.6	42	9.8
40 (39)	8.5 (12.9)	44	13.1
42	7.1	46	5.4
52	8.1	47	12.7
54	11.0	et 48 L	15.3
54	10.4	53	10.5
62	11.8	54	10.5

Figure 2

Breathing air before breathalyzer (ppm)*	Blood carboxy-hemoglobin (% COHb)	Breathing O_2 in transit before breathalyzer (ppm)*	Blood carboxy-hemoglobin after O_2 (% COHb)
64	10.4	56 (5) X	8.5
68	13.2	56	11.0
70 (72)	18.4 (18.4)	62	8.8
85	9.0	62	6.6
90 (93)	16.0 (14.0)	64	8.1
103 (104)	28.4 (26.8)	69	9.3
107	13.5 (11.8)	73	10.4
		78	10.1
		82 (122) X	10.1
		84	15.8
		99	12.9
		102	10.6
		118	12.6
		147 L	11.7

duplicates samples or tests are in parentheses * = parts per million L = influential observation
et = oxygen administered by ET tube X = Outlier duplicate

The correlation between alveolar CO and venous blood %COHb was statistically significant after adjusting for oxygen effects ($p < 0.000$). The patients breathing air had a regression curve that was almost identical to the Stewart curve, but those breathing oxygen differed ($p = 0.009$). Fig. 1 shows a scatterplot of the 43 patients used to calibrate the process. The Stewart curve and the "Air Only" curve were almost indistinguishable on the graph. The curve for oxygen treatment lies somewhat below the air curve. The pooled standard deviation of the models was 3.115, which produces a 95% confidence interval for the estimated %COHb of ± 6.30. Figs. 2 and 3 show the breakout of the two curves with their associated data points to better illustrate how each curve fits its own data set. The influential observations have been plotted and labeled in Figure 3 for completeness. The points tagged as "Lever" are the two that had significant leverage on the curve. It can be seen that these two points would lift the left side of the curve and depress the right side.

Figure 3

Figure 1: Emergency setting, the 43 calibration patients. Carbon monoxide (parts per million) in breath versus venous carboxyhemoglobin (%). Calibration data from this study.

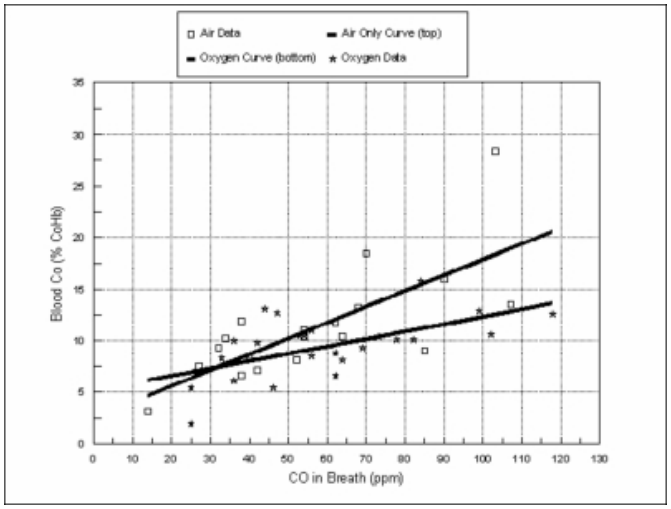


Figure 4

Figure 2: Emergency setting, 19 patients breathing air before breathalyzer. Carbon monoxide (parts per million) in breath versus venous carboxyhemoglobin (%).

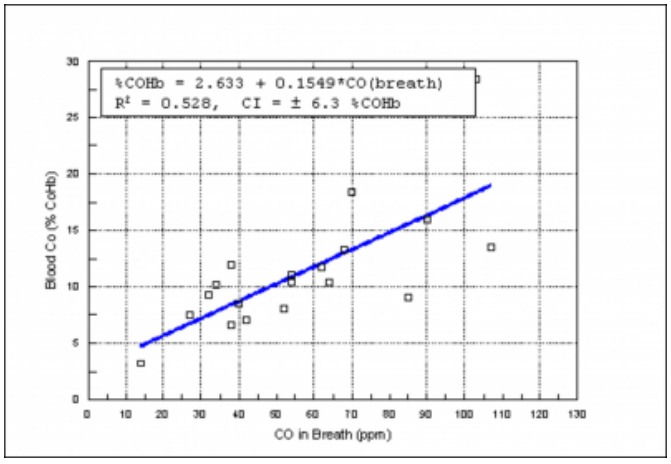
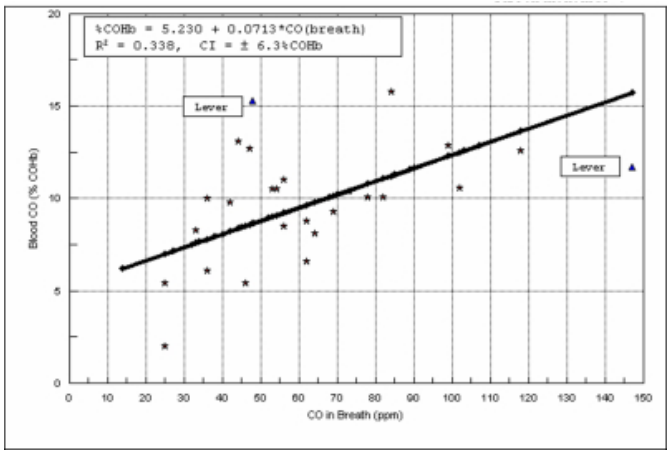


Figure 5

Figure 3: Emergency setting, 26 patients given oxygen in transit before breathalyzer. Carbon monoxide (parts per million) in breath versus venous carboxyhemoglobin (%). Influential observations included. Lever = Influential value that would leverage curves away from preponderance of data.



COMPARATIVE SUMMARY

The equations for the various studies are summarized for easy comparison:

Breathing air

1. Stewart curve: COHb = 2.902 + 0.1549(CO-breath)-0.001(CO-breath)2,

R-sq = 0.9965 CI = ± 0.5 %COHb (theoretical)

2. Jarvis curve: COHb = 0.630 + 0.1600(CO-breath),

CI = ± 1.6 %COHb (laboratory)

3. Fife/Otto curve: COHb = 2.633 + 0.1531(CO-breath),

R-sq = 0.5384 CI = ± 6.3 %COHb (emergency setting)

Note that the slopes are all essentially the same; only the intercept of the Jarvis curve differs.

Breathing oxygen

4. Fife/Otto curve: COHb = 5.230 + 0.0713(CO-breath),

R-sq = 0.338 CI = ± 6.3 %COHb (emergency setting)

A SIMPLIFIED METHOD USING CUT-OFF SCORES

The research reported above has established a preliminary empirical relationship between the breathalyzer readings and the %COHb determinations. There is a high probability that

the response curves are different for oxygen and air breathing during transit. Equations and curves, however, are not well suited for use in an emergency setting. Simple cut-off scores are superior if they provide sufficiently high reliability with low false positive and negative rates. This approach was pursued with each of the data sets (air and oxygen) without deleting influential observations.

In nonsmokers, COHb levels are usually considered elevated if they are above 3%; however, the %COHb of smokers can approach 9%. To facilitate analysis, the cut-off point between low and high risk patients was defined for the purpose of this study to be 10%COHb. Tabulations of the data determined that the best breathalyzer cut-off scores for patient classification were 53 for air and 43 for oxygen. Table 2 shows the tabulations and the statistics for each of the two data sets. A false positive is the classification of a person to be high risk when he is not; false negative is to classify a person as low risk when he is actually high risk.

Figure 6

Table 2: Cut-off Score Performance

	Air Cut-off Score, ppm			Oxygen Cut-off Score, ppm		
% COHb	Breath < 53	Breath > 53	Total	Breath < 43	Breath > 43	Total
# 10	7	1	8	6	6	12
> 10	2	9	11	0	14	14
Total	9	10	19	6	20	26
Statistics Pearson Chi Square = 8.9266, p-value = 0.003 % Correct = 16/19 = 84.2% % False Negative = 2/9 = 22.2% % False Positive = 1/10 = 10%				9.1000, p-value = 0.003 20/26 = 76.9 % 0/6 = 0.0% 6/20 = 30.00%		

DISCUSSION

In this study, the breath CO concentration was compared with %COHb measured in venous blood samples drawn less than 10 minutes after the breath test. Because strong correlation between arterial and venous %COHb values has already been demonstrated ($_{8}$), venous blood can be used; there is no need for arterial puncture. Animal studies have shown that CO binds directly to intracellular hemoproteins. COHb values indicate exposure to CO but do not correlate consistently with symptoms or prognosis ($_{9}$). This should also be true for exhaled CO.

Standard blood gas analyzers cannot be used to establish the diagnosis of CO poisoning because they measure pH and the partial pressures of O2 and CO2 and then calculate the hemoglobin O2 saturation from these values. By that method, oxygen saturation will appear to be normal even in the presence of significant CO poisoning. CO-oximeters, however, measure the absorbency of a sample hemolysate at four wave lengths, and can electronically calculate COHb, total hemoglobin, methemoglobin, and the percent hemoglobin by solving four simultaneous equations using absorption coefficients stored in memory ($_{10}$). The cost of purchasing a CO-oximeter is highly variable but may exceed $16,000 compared to about $1400 for the portable breathalyzer, a difference of more than ten to one. CO-oximeters are not available in all U.S. hospitals. How many hospitals do not have the equipment needed to diagnose the most common cause of poisoning death in the United States is not known. Pulse oximetry cannot detect a decrease in hemoglobin saturation due to COHb ($_{11}$). Not only are breathalyzers considerably less expensive and non invasive, they can be used by emergency medical personnel during transport to make an early diagnosis with a false negative rate of only 8% in this set of data.

Hand-held breath CO monitors contain an electrochemical CO sensor composed of sensing, counter, and reference electrodes separated by a thin layer of electrolyte. The gas diffusing to the sensing electrode reacts at the surface by oxidation, and the sensing electrode reacts with CO to create an electrical charge that is then measured and converted into a ppm reading. The reaction is CO + H2O CO2 + 2H + + 2e-. The Bedfont instrument has an organic filter that may prevent inaccuracies caused by other breath components such as alcohol or ketones, although these substances may still represent a source of false positive results that our study was not designed to evaluate. Also, the variation in our data may be caused in part by the difficulty in obtaining consistent alveolar breath samples in the emergency setting. It is possible that rapid, shallow breathing could decrease the accuracy of breath testing. In most emergency centers, circumstances for sample collection will be less than ideal, and similar variations should be anticipated in either hospital or field use. Some reduction in variation can also be expected as emergency medical technicians become more skilled in the measurement process.

Estimates of COHb based on breath tests must be calibrated over a wide range of readings to assess the relationships likely to be encountered in CO poisoning. Because our data were collected in an emergency setting, few repeat measurements could be taken. Our data conformed closely with the Stewart curve for air-breathing patients, but the reported precision of ± 0.5% COHb was not observed. Our data suggest that ± 6.3% COHb is a more likely norm in an emergency setting. The lower variability of the Jarvis data is probably because samples were taken from volunteers in a relaxed environment. The difference in the intercept value of

the Jarvis equation may be related to instrument calibration because the slopes are essentially the same. Also, our data do not support the Jarvis finding that the CO in the second breath sample was uniformly greater than the first.

Inhaled CO readily diffuses across the alveolar-capillary membrane. The rate of CO off-gassing by the pulmonary capillary bed with respect to time is a function of many physiologic variables including alveolar ventilation, the partial pressures of oxygen and carbon dioxide in the alveolar gas, the pulmonary diffusing capacity, the rate of endogenous CO production, the partial pressure of carbon monoxide in the blood, and perhaps many other factors. This study was not designed to evaluate any of these variables since blood gases, cardiac output, ventilation perfusion ratios and other important physiologic parameters were not measured in the emergency setting. We did find strong evidence that patients breathing oxygen have a different response curve than those breathing air. This seems reasonable because if oxygen is effective in reducing the CO in the blood, each breath should be removing more CO. This effect will yield a higher breath CO ppm and shift the curve to the right. The effect seems to be proportional to the CO concentration in the blood and hence the difference between the two curves is greater at higher %COHb.

CONCLUSIONS

In utilizing a screening device, the greatest danger lies in underestimating the %COHb because this could result in failure to appreciate the severity of poisoning. While our data conform well with the Stewart curve for air-breathing patients, a precision of ± 6.3% COHb is a more likely norm in an emergency setting. Our findings also suggest that there is a different relationship between patients breathing air and those breathing oxygen just before sampling. A cut-off score of 43 ppm for oxygen breathers and 53 ppm for air breathers may be used for rapid classification of “high risk” patients (patients whose COHb is likely to be 10% or higher) with a reliability of 77% for oxygen breathers and 84% for air breathers. The cut-off score performance compares favorably with other screening studies, with an overall false negative rate of only 13.3 % (2 of 15) and a false positive rate of 23.3% (7 of 30). In addition, 23 of 25 patients (92%) with %COHb > 10% were correctly identified. These data indicate that portable breathalyzers can provide fast, inexpensive, and noninvasive estimates of the approximate concentration of blood COHb, facilitating diagnosis and treatment of CO poisoning.

Since this was a pilot study, project review suggests that precision could be increased with better written procedures, training of EM personnel, and the taking of duplicate samples on all patients. When a discrepancy of more than (10ppm exists between breathalyzer readings, a third breath sample should be taken to isolate the outlier value.

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