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Correlation between clinical severity and different non-invasive measurements of carbon monoxide concentration: A population study

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Abstract

Objectives

Carbon monoxide (CO) poisoning is a major concern in industrialized countries. Each year, thousands of victims, resulting in approximately 100 fatalities, are encountered in France. The diagnosis of CO poisoning is challenging; while carboxyhemoglobin (COHb) may be useful, it is a weak indicator of the severity of CO poisoning. This weak indicator may be a result of the delay between poisoning occurrence and the blood assay. Two apparatuses, CO oximeters and exhaled CO analyzers, now permit COHb to be determined outside hospitals. Our hypothesis is that these instruments allow the early measurement of COHb concentrations, which are more correlated with the severity of poisoning, expressed using the poisoning severity score (PSS).

Design

In an observational and retrospective cohort study, the distribution of COHb measurements obtained by CO oximetry or by exhaled CO analyzers was compared between groups of severity expressed using the PSS.

Setting

Data were collected in the Paris area from January 2006 to December 2010 by the French Surveillance System of CO poisoning.

Participants

All patients with CO poisoning reported to the French Surveillance System of CO poisoning.

Results

There was a significant difference in the COHb values obtained by CO oximetry between groups stratified according to PSS ($p<0.0001$). A significant difference in the values of exhaled CO was also observed between PSS groups ($p = 0.006$), although the relationship was not linear.

Conclusions

The COHb concentrations measured using CO oximetry, but not those measured using exhaled CO analyzers, were well correlated with the severity of CO poisoning.

Introduction

Carbon monoxide (CO) poisoning is the most common cause of accidental poisoning in France with approximately 4000 cases per year reported by the French CO Poisoning Surveillance System [1]. Consequences may be severe and include transient neurological symptoms, coma, respiratory and cardiovascular failure, and death. The diagnosis of CO poisoning is based on unspecific clinical features, measurement of carboxyhemoglobin (COHb) in the blood, and discovery of CO in the atmosphere on site. However, COHb is not correlated with the severity of CO poisoning [2] or with the occurrence of delayed neurological sequel (DNS) [3]. The delay between the end of exposure and measurement and the application of oxygen therapy before measurement are often cited to explain the lack of correlation. In France, the first responders (firefighters or emergency medical personnel) are now often equipped with CO breath analyzers or CO oximeters. These two apparatuses can provide information about CO poisoning levels without the need for a blood sample and within a short time after CO exposure. The CO breath analyzer provides the CO concentration in exhaled air, which is well correlated with low COHb values (<40%) [4]; however, it tends to underestimate high values [5]. CO oximeters allow the non-invasive measurement of COHb with precision between 2% and 6% [6–8]. These new instruments can allow the early determination of COHb, which may be more correlated to severity. The objective of this study was to evaluate the correlation between measurements obtained using breath analyzers or via CO oximetry and clinical severity among patients with CO poisoning.

Methods

This study is an observational and multicenter cohort study. Data were provided by the French CO Poisoning Surveillance System coordinated by the Institute of Health Surveillance ("Institut de Veille Sanitaire—InVS") to which cases of CO poisoning are declared. Any suspected or confirmed intoxication is reported to the health authority (regional health agency or anti-poison centre by delegation). Variables were assessed by the physician treating the victims of CO poisoning in an emergency room or in any hospital department. And a public health doctor of the regional health agency or anti-poison center collected the data using a standardized medical form. They send these forms on a web application to constitute the epidemiological database exploited by the French Surveillance System of CO poisoning. The French data protection agency ("Commission Nationale de l'Informatique et des Libertées—CNIL") approved this retrospective study, and the data were completely anonymous in accordance with French regulation (approval number: 1375107). All cases of CO poisoning in Paris and

suburbs reported to the French CO Poisoning Surveillance System from January 2006 to December 2010 were included. CO poisoning cases that were fire-related were excluded because toxins other than CO (e.g., cyanide) could have been involved. The data collected included demographic data (sex and age), pregnancy status, smoking status, and initial clinical features. The initial clinical features included headache, asthenia, nausea/vomiting, vertigo, transient loss of consciousness, transient palsy, dyspnea, coma, pulmonary edema, chest pain, ventricular arrhythmia, myocardial infarction, seizure, circulatory failure, rhabdomyolysis, severe acidosis, brain stroke, and death. The severity of the poisoning was established using the modified Poisoning Severity Score (PSS) developed by the European Association of Poison Centres and Clinical Toxicologists [9]. The modified PSS introduces a sixth grade, differentiating transient loss of consciousness and transient palsy from coma and stroke; this allows each patient to be classified into one of 6 severity grades: asymptomatic, 0; minor, 1; moderate, 2; intermediate, 3; severe, 4; and fatal, 5 (Table 1). Data regarding the nature of the treatment (normobaric or hyperbaric oxygen therapy) were also collected. Finally, the value of the biomarker with CO was collected before or after initiation of oxygen therapy. The value by CO oximetry was expressed as a percentage of the total hemoglobin concentration. Exhaled CO was expressed as ppm, and the value expressed by the blood COHb assay was expressed as a percentage of the total hemoglobin concentration.

The data provided by the InVS were anonymous; thus, it was impossible to check or obtain other information from the medical record of patients.

Quantitative results were expressed as medians with interquartile ranges and qualitative results as percentages. Univariate comparisons were made using the exact Fisher test (for qualitative or discrete variables) or the Wilcoxon rank sum test (for continuous variables). Then, the distribution of CO impregnation was compared between groups of increasing clinical severity, i.e., severity grade, by a non-parametric Kruskal-Wallis test. To control for the potential confounding effect of smoking, we further adjusted these comparisons on smoking status, using a linear model. All p-values were two-sided, with $p<0.05$ denoting statistical significance. The statistical analysis was performed using R® v2.15.2 (http://www.R-project.org/).

Results

The study included 3153 patients. Table 2 shows the patient and CO measurement characteristics. The median age was 31 (interquartile range, 13–44) years. Fifty one percent of patients were female. Smoking status was available in 2060 patients with 1685 (53%) being non-smokers and 375 (12%) being smokers. A total of 125 (3.9%) patients were lost to follow-up after intoxication. Among the 3028 remaining patients, 31 (0.98%) died, with death occurring at the place of the intoxication in 15 patients (including 3 after the first responders arrived), in the hospital in 6 cases, and at unknown locations in the remaining 10 cases. Of those treated with oxygen, 2196 patients received treatment with normobaric oxygen alone, and 408 patients

Table 1. Poisoning severity score (adapted from Persson et al. [9]).

Grade	Sign
0	None
1	Asthenia, headache
2	Nausea / vomiting, vertigo
3	Transient loss of consciousness, transient palsy, dyspnea
4	Pulmonary edema, chest pain, ventricular arrhythmia, myocardial infarction, seizure, circulatory failure, rhabdomyolysis, severe acidosis, brain stroke
5	Death

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Table 2. Patient and CO measurement characteristics.

Characteristic		Number of patient	% or median [IQR]
Population		3153	
Age (years)		2948	31 [13–44]
Gender	male	1501	49%
	female	1560	51%
	unknown	92	
Smoking status	no	1685	53%
	yes	375	12%
	unknown	1093	35%
Clinical severity	0	1543	49%
	1	848	27%
	2	485	15%
	3	209	7%
	4	37	1%
	5	31	1%
Exhaled CO measurement		94	3%
Exhaled CO (ppm)	all	94	51.5 [10–137]
	before oxygen therapy	64	72.50 [12.75–144.8]
	after oxygen therapy	4	43 [7.5–124.5]
	unknown	26	22.50 [6.25–113.8]
CO oximetry measurement		90	3%
CO oximetry (%COHb)	all	90	15.85 [8–24.3]
	before oxygen therapy	23	16 [11–26]
	after oxygen therapy	58	15.35 [8–22]
	unknown	9	16 [12–26]
Blood assay measurement		2328	74%
Blood assay (%COHb)	all	2327*	8 [3.6–14.3]
	before oxygen therapy	1382	8.9 [4.1–15.2]
	after oxygen therapy	495	7.5 [3.5–13.9]
	unknown	451	6.4 [2.2–11]
Evolution	alive	2997	95%
	deceased	31	1%
	unknown	125	4%
Place of death	out of hospital before first responder arrival	12	57%
	out of hospital after first responder arrival	3	14%
	in hospital	6	29%
Hospitalization	no	2470	79%
	yes	606	19%
	unknown	77	2%

Data are median [Q1; Q3] or number of patients (%);

*: one patient had a blood assay performed but the value was missing.

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received treatment with hyperbaric oxygen. The remaining 443 patients received no oxygen therapy.

The PSS was 0, 1, 2, 3, 4, and 5 for 1543 (48.9%), 848 (26.9%), 485 (15.4%), 209 (6.6%), 37 (1.2%), and 31 (1%) patients, respectively.

Among the 3153 patients included, COHb was measured using blood samples in 2328 (73.8%) cases, CO was measured in exhaled breath 94 (3%) cases, and COHb was measured by CO oximetry in 90 (2.9%) cases. Some patients underwent two types of assessment. There were 715 (22.7%) patients who did not undergo any assessment (Fig 1).

Patients whose COHb concentrations were measured by CO oximetry were significantly more often smokers (18.9% vs 11.7%) and lost consciousness more frequently (12.2% vs 6.4%) than patients whose COHb concentrations were not measured by CO oximetry. There was a difference in the results of COHb by CO oximetry between the PSS groups ($p<0.0001$ by Kruskal-Wallis test) (Fig 2). This difference remained significant after adjustment for smoking status.

Patients in whom CO in exhaled breath was assessed were significantly older (median age, 36 vs 31 years) and less often smokers (4.3% vs 12.1%) compared to those in whom CO in exhaled breath was not assessed. There was a significant difference in the results of exhaled CO between PSS groups ($p = 0.006$ by Kruskal-Wallis test), although the observed relationship appeared to be not linear (Fig 3).

Patients whose blood samples were used for COHb assessment were significantly more often smokers (13.4% vs 7.5%) and more frequently lost consciousness (7% vs 5.2%) than patients whose blood samples were not used for COHb measurement. There was a significant difference in the values of COHb between PSS groups ($p<0.0001$ by Kruskal-Wallis test) (Fig 4). The difference remained significant after adjustment for smoking status.

Discussion

To our knowledge, no previous clinical study found a strong correlation between CO values measured by CO oximetry and the clinical severity of CO poisoning. This is the first study to identify such a correlation. CO oximetry provides an objective indication of the clinical severity of poisoning. Therefore, during the initial clinical assessment, CO oximetry could help to identify the most severe poisoning cases. In cases of mixed intoxication such as those noted in cases of suicide attempts with inhalation of exhaust gases and drug absorption, CO oximetry could help to distinguish the different toxins involved.

No study has evaluated the accuracy of measuring COHb with CO oximetry in cases of circulatory failure. In our study, the COHb values obtained for severity group 3 by oximetry were higher than those obtained for group 4 (28.25% and 26.3%, respectively). Although this difference is not significant, it is possible that the hemodynamic failure induced an underestimation of COHb by CO oximetry, as already reported for oxyhemoglobin by standard pulse oximetry [10].

No significant correlation was found in this study between exhaled CO concentration and clinical severity before clinical oxygen therapy regardless of the smoking status. The mean concentration of exhaled CO was even lower in groups 3 and 4 than that in groups with lower severity. Lapostolle et al. found a correlation between exhaled CO values and clinical severity [11]. The main hypothesis to explain these conflicting results is that the procedure needed to obtain a good measurement of exhaled CO was not controlled in this study, whereas it was controlled in the study by Lapostolle et al. Although the methodology of Lapostolle's study implied that the measurement was performed appropriately, this measurement requires the achievement of apnea for 20 seconds and full expiration into the manifold. Patients with CO poisoning suffering from neurological impairment cannot comply with complex techniques of breath analysis. Therefore, this technique will be inappropriate in such patients. In contrast, CO oximetry does not rely on the patient's cooperation and therefore can be used on CO poisoning patients with neurological impairment and non-cooperative patients such as children.

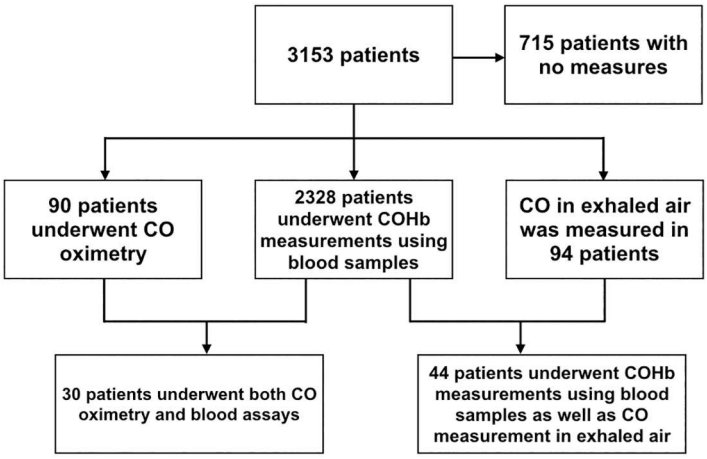

Fig 1. Flow chart showing the types of assays performed.

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A few limitations should be highlighted. The delay between the end of exposure to CO and the measurement of CO levels (by breath analyzer or CO oximetry) was unknown. This is explained by the limited data provided to us by the InVS. Consequently, the levels may have been underestimated compared to the initial level. However, the patients included in this study lived in an urban area. Hence, the delay should have been short. As the half-life of COHb is approximately 4 hours when breathing air, we suppose that measurements obtained before oxygen therapy were sufficiently accurate. Despite the large number of patients included, fewer than 100 measurements were available for each technique. The reason may be the poor availability of those techniques or missing data in the CO poisoning case reports. Another explanation is that those techniques are used more often onsite by emergency medical teams than in emergency departments where standard oximetry using blood samples is available. Usually, patients with CO poisoning do not need an emergency medical team onsite and are transported to an emergency department by first responders (mainly firefighters in France).

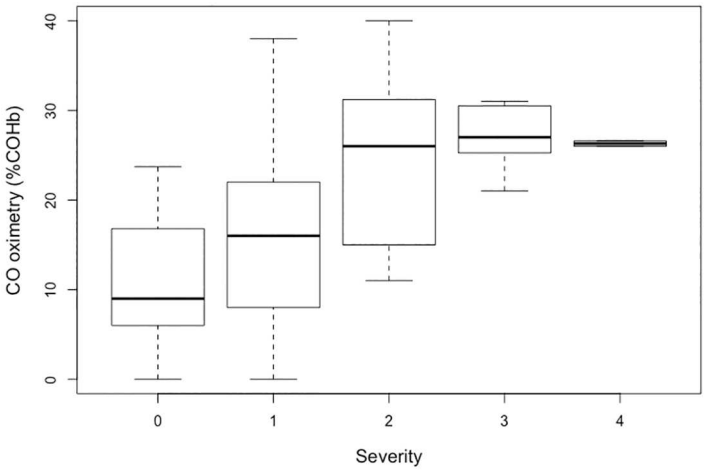

Fig 2. Relationship between COHb measured by CO oximetry (in %) and PSS.

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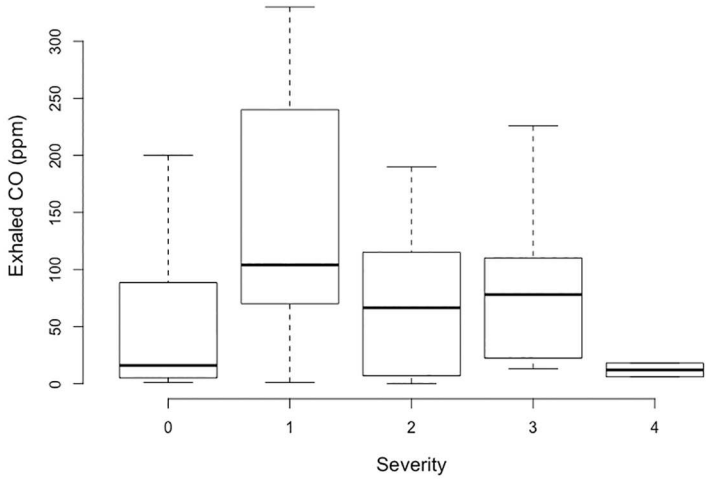

Fig 3. Relationship between exhaled CO (in ppm) and PSS.

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The first study on the correlation between the COHb concentration and symptoms of CO poisoning dates back to the late 19th century. Haldane [12], Sayers [13], and Killick [14] performed experimental studies on a small number of healthy volunteers (1 healthy volunteer for Killick, 3 for Sayers, and Haldane practiced the study on himself). These authors concluded that there was a good correlation between symptoms and COHb concentration. However, clinical studies assessing correlations between COHb concentration and the clinical severity of CO poisoning have used varying methods with contrasting results. Roche et al. found that COHb concentrations higher than 50 ml/L were associated with poorer prognosis than lower values [15]. Norkool [16], Blettery [17], Mathieu [18], and Meulemans [19] found a significant difference in carboxyhemoglobin level between patients who did or did not lose consciousness. However, Sokal [20], Burney [21], and Fang [22] did not find any significant correlation between clinical severity and COHb concentration. In most of these studies, the time elapsed between CO exposure and performance of the COHb blood assay was unknown, as was the duration between treatment initiation and the time of measurement. The time interval

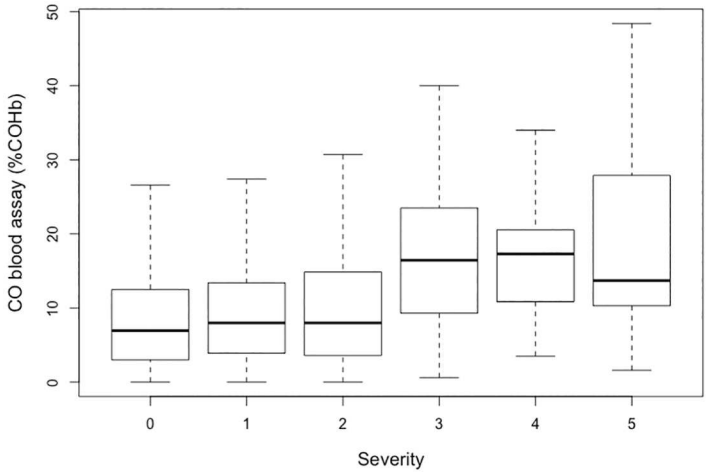

Fig 4. Relationship between COHb measurement by blood assay (in %) and PSS.

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between exposure and measurement is probably the main explanation for the lack of correlation found in the literature with respect to our study.

Conclusion

In cases of CO poisoning, COHb concentrations measured by CO oximetry strongly correlated with clinical severity. No significant correlation was found between values of exhaled CO and clinical severity, probably because of the more restrictive measurement technique especially among patients unable to comply with breath analyzers procedure. CO oximetry should be prioritized over the use of breath analyzers for diagnosing CO poisoning in emergency departments and first responder units.

Supporting information

S1 Dataset. Data study. Anonymized data from the study, case number and year of poisoning have been erased for confidentiality purpose.
(XLS)

Author Contributions

Conceptualization: TH JA DA.

Data curation: TH KD SC.

Formal analysis: KD SC.

Investigation: TH JA DA.

Methodology: KD SC DA.

Project administration: DA.

Resources: JA.

Supervision: DA.

Validation: DA.

Visualization: TH.

Writing – original draft: TH.

Writing – review & editing: TH KD SC DA.

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