Review Article

Carboxyhemoglobin: a primer for clinicians

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ABSTRACT

One of carbon monoxide's several mechanisms of toxicity is binding with circulating hemoglobin to form carboxyhemoglobin, resulting in a functional anemia. While patients with carbon monoxide poisoning are often said to be "cherry-red," such discoloration is rarely seen. Carboxyhemoglobin levels cannot be measured with conventional pulse oximetry, can be approximated with pulse CO-oximetry, and are most accurately measured with a laboratory CO-oximeter. Carboxyhemoglobin levels are quite stable and can be accurately measured on a transported blood sample. For clinical purposes, arterial and venous carboxyhemoglobin levels can be considered to be equivalent. Carboxyhemoglobin levels are typically lower than 2% in non-smokers and lower than 5% in smokers. A level over 9% is almost always due to exogenous carbon monoxide exposure, even among smokers. Conversely, a low level does not exclude significant exposure under certain circumstances. As carboxyhemoglobin levels of poisoned patients do not correlate with symptoms or outcome, their greatest utility is a marker of exposure.

What is carboxyhemoglobin?

Carbon monoxide (CO) is a byproduct of combustion, resulting from the incomplete oxidation of carbon to the CO molecule instead of the carbon dioxide (CO_2) molecule that is produced when oxidation is complete [1]. Carbon monoxide is a gas, insensible to humans. It has no color, taste or smell [1]. Odors from gases containing carbon monoxide, such as motor vehicle exhaust, are the result of other hydrocarbon by-products of combustion.

When CO is inhaled, it travels to the alveoli, crosses the alveolar-capillary membrane and binds to hemoglobin in circulating red blood cells [2]. It binds in the same iron-containing sites to which oxygen binds. However, CO binds with an affinity 200-250 times greater than oxygen [3]. Hemoglobin bound with CO is known as carboxyhemoglobin (COHb). The majority of circulating COHb is the result of exogenous exposures, but endogenous production of CO does typically account for a small amount of COHb.

Cherry red?

In 1857, Hoppe in Germany first noted that blood containing carboxyhemoglobin is a brighter shade of red than non-CO laden blood [4]. Some have referred to this shade as "cherry red" and described the color of skin and mucous membranes of those with high COHb levels as appearing cherry red. This is based on the concept that blood flowing through cutaneous capillaries contributes to an individual's skin color. Confounding the attempt to compare the color of COHb to cherries is the fact that there are many varieties of cherries, and they come in a wide range of colors [5].

Even if it were possible to identify a particular strain of cherries as being most similar to the color of carboxyhemoglobin, the color difference between COHb and oxyhemoglobin (HbO_2) is subtle (Figure 1). Experts agree that the COHb level would need to be extremely high to expect to see a change in skin color. As such, most individuals with "cherry red" discoloration from CO poisoning are deceased (Figure 2). The physician most likely to encounter a cherry red patient is the pathologist. In fact, the red discoloration of internal organs from an individual dying of CO poisoning is often much more striking than skin changes (Figure 3).

The finding of red skin discoloration from high levels of COHb is neither 100% sensitive nor specific for CO poisoning. Among individuals dying of CO poisoning, fewer than one-half have red skin as measured by reflectance spectrophotometry [6]. The post-mortem presence of COHb in cutaneous capillaries is dependent upon blood distribution and pooling after death. Plus, not all individuals with red skin have high COHb levels. For example, treatment for cyanide poisoning with the

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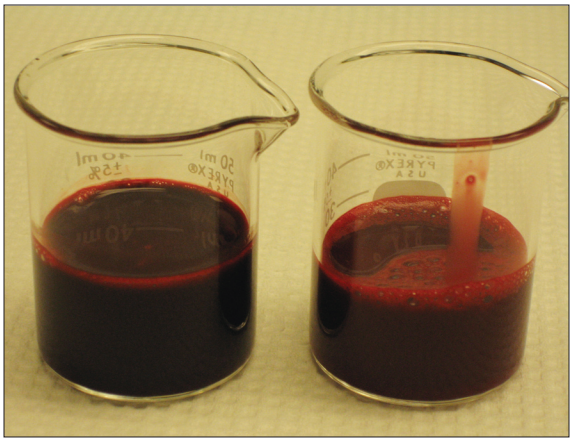

FIGURE 1.
The author's anticoagulated blood, at baseline and after bubbling carbon monoxide through a sample. Carboxyhemoglobin levels by laboratory CO-oximetry were 1.5% for the sample on the left and 94.4% for the sample on the right.

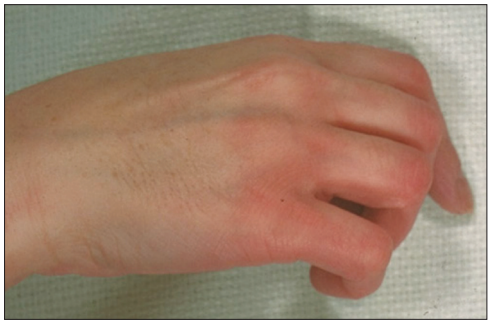

FIGURE 2.
Cutaneous red discoloration in a case of fatal carbon monoxide poisoning. *(Photo courtesy of Dr. James Caruso)*

FIGURE 3.
Autopsy jars holding organs of an individual who died of carbon monoxide poisoning and one who did not. *(Photo courtesy of Dr. James Caruso)*

antidote hydroxocobalamin can cause skin to appear bright red for up to two weeks after administration [7].

Using color to measure carboxyhemoglobin

The clinical use of blood color as a comparator for specific COHb levels dates well into the last century. In an interesting application of portable COHb measurement, Sayers and Yant published in 1925 a method for field processing of blood samples to measure levels in mine workers underground [8]. They developed a portable kit wherein a 0.1-ml finger stick blood sample was suspended in water, then processed in a prescribed way and compared to a set of standard colors. The colors corresponded to various COHb levels in blood processed by the same method (Figure 4). Sayers and Yant claimed the technique had accuracy within 5%. This author's reproduction of their technique is shown in Figure 5. Accurately assigning a COHb level based upon selection of the most closely matching color would certainly require expertise.

The bright red color of COHb results from the fact that the absorption spectrum of COHb is different from that of either HbO_2 or deoxyhemoglobin (Hb) (Figure 6) [9]. This is the basis for routine laboratory measurement of COHb concentration in the blood. If a multiwavelength spectrophotometer (CO-oximeter) is used to transmit several wavelengths of light through a sample of blood of known path length, levels of the hemoglobin species can be determined based upon known relative absorbance at different wavelengths. In essence, the "color" of the blood is used to determine the COHb level.

Another example using the "color" of blood to estimate COHb levels is fingertip oximetry. A conventional pulse oximeter measures the change in light absorbance that occurs during the pulsatile phase of blood flow and calculates the absorbance by HbO_2 relative to Hb to yield arterial blood oxygen saturation (SpO_2) [10]. It is possible to do this with only two wavelengths of light (typically 660 and 990 nm) because of differences in the absorption spectra (color) of HbO_2 and Hb, and the assumption that the change in light absorption during pulsation is solely due to HbO_2 and Hb. Carboxyhemoglobin has an absorption spectrum similar to HbO_2 at one of the two wavelengths used by pulse oximeters (660 nm) and therefore tends to be "seen" somewhat similarly, but not totally, as oxyhemglobin

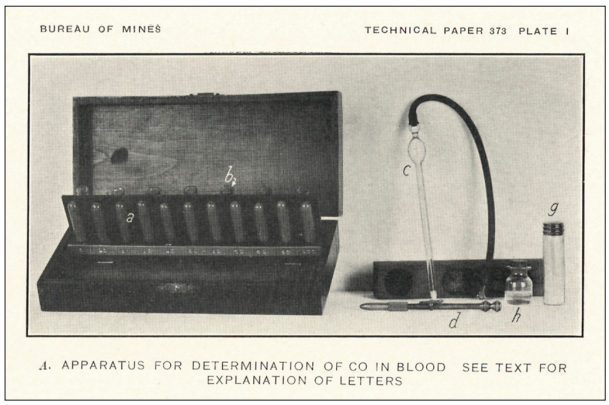

FIGURE 4.
Portable kit developed by Sayers and Yant in 1925 to measure carboxyhemoglobin levels in miners on site using the pyrotannic acid technique. Miners' finger stick blood samples were processed by a specified method, then compared to the standard vials shown to determine COHb levels [8].

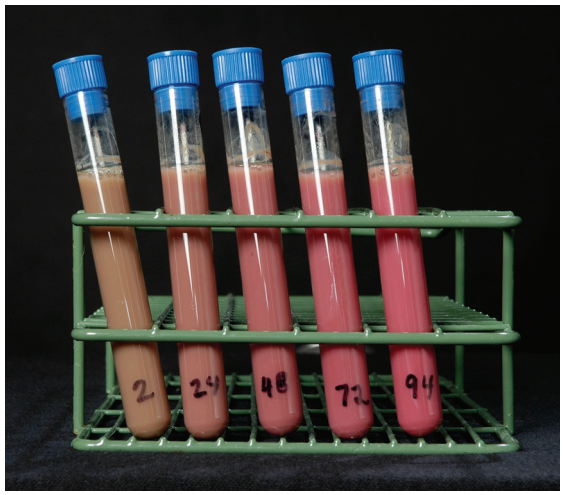

FIGURE 5.
Vials of blood prepared by the author using the pyrotannic acid method of Sayers and Yant [8]. Carboxyhemoglobin levels from left to right are 2%, 24%, 48%, 72% and 94%.

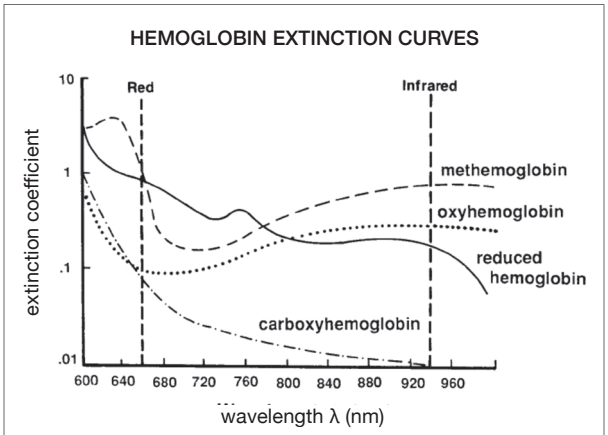

FIGURE 6.
Absorption spectra of four hemoglobin species.

[9,11]. The presence of an interfering substance can only be appreciated with extremely high COHb levels over 40%-50% [11]. A multiwavelength fingertip oximeter capable of separating COHb from HbO_2 and thereby estimating the percentage of COHb present in circulating blood was released in 2005 [12]. The portable pulse CO-oximeter is capable of measuring both blood carbon monoxide saturation (SpCO) and SpO_2 in vivo. A number of investigators have measured the variation between SpCO and corresponding COHb levels from a laboratory CO-oximeter and published their results [13-16]. It should not be surprising that differences between the two techniques exist when one considers the added variables involved when transmitting light through a fingertip as compared to an ex-vivo blood sample in a cuvette in a controlled laboratory environment (e.g., motion, varying path length, ambient light).

For clinical purposes, arterial and venous COHb levels are similar, and the measurement can be made on either type of blood sample [17,18]. COHb levels have been demonstrated to be stable for four weeks in stored blood, even when not refrigerated [19]. If a better estimate of peak COHb level than that obtained upon emergency department (ED) presentation is desired, an anticoagulated blood sample can be obtained at the site of CO poisoning and forwarded with the patient. Use of a green-top vacutainer tube containing sodium- or lithium-heparin anticoagulant is recommended for compatibility with the greatest number of commercially available laboratory CO-oximeters [19].

'Functional anemia' and carboxyhemoglobin

Carbon monoxide has a number of mechanisms of toxicity, one of which has been called the "functional anemia" resulting from carboxyhemoglobin formation. In 1857, Claude Bernard first proposed the concept that CO toxicity was mediated by COHb formation [20]. Avid binding by CO to hemoglobin competitively prevents oxygen from binding as red blood cells pass through the pulmonary vasculature. Arterial blood oxygen content is thereby reduced and peripheral

TABLE 1. Carboxyhemoglobin levels in various populations, as well as extreme reported levels

CONDITION (citation)	CARBOXYHEMOGLOBIN level	
Never smokers (22)	0.83 ± 0.67% (n = 5,459)	95th percentile 1.65%
Rural	0.74 ± 0.61% (n = 1,999)	
Urban, not central city	0.91 ± 0.70% (n = 719)	
Urban, central city	1.11 ± 0.69% (n = 629)	
Smokers (22)	4.30 ± 2.55% (n = 2,533)	95th percentile 8.68%
CO-poisoned patients treated with HBO_2 (28)	23.4 ± 10.4% (n = 1,392)	range 0.1 – 77.0%
CO poisoning deaths (35)	66 ± 17% (n = 1,233)	range 3 – 98%
Highest reported survived level (33)	73%	
Highest reported level (35)	98%	

oxygen delivery potentially impacted [2]. As an example, raising the blood COHb level from 1% to 50% reduces the oxygen-carrying capacity by approximately one-half ("functional"), similar in magnitude to a reduction in hematocrit from 40% to 20% (anemia). Further, COHb formation results in a leftward shift of the HbO_2 dissociation curve [21], causing oxygen molecules to bind more tightly to available hemoglobin sites and thereby making peripheral unloading of oxygen to the tissues more difficult. The immediate compensatory physiologic response to the functional anemia of CO intoxication is an increase in cardiac output to maintain tissue oxygen delivery.

Carboxyhemoglobin levels – averages and records

Since COHb levels are expressed as a percentage of the total hemoglobin, COHb concentration could theoretically range from 0%-100%. Many are surprised to learn that the normal level is not 0%. In 1982, Radford and Drizd published data from 11,368 individuals aged 3-74 years selected to participate in the carboxyhemoglobin portion of the second National Health and Nutrition Survey (NHANES II) (Table 1) [22]. They found that among "never" smokers, COHb averaged 0.83 ± 0.67% (mean ± SD). The 50th and 95th percentiles were 0.72% and 1.65%, respectively. This slight elevation above zero relates to exposure to CO in the environment (Table 1), as well as endogenous production of CO. Endogenous production is due largely to heme degradation. When heme is broken down, one heme molecule produces one molecule of CO [23], resulting in a basal COHb level of about 1%. The extreme example of endogenous CO production occurs in hemolytic anemia. With hemolysis in non-smokers with sickle cell disease, COHb levels in the range of 3.5%-4.3% have been reported [24-26]. Non-sickle cell hemolysis has resulted in measured COHb levels of 4.5% in malaria [27], 7.3% with antibiotic-associated hemolytic anemia [28] and 9.7% in sepsis [29].

In the NHANES II data, 2,553 current smokers aged 12-74 years had an average COHb level of 4.3 ± 2.6% [22]. The 95th percentile of COHb in smokers was 8.7%. This suggests that if a COHb level is greater than 9%-10%, a source other than cigarettes should be sought, even among smokers. The COHb level in smokers is generally in the 3%-5% range [30]. Also from the NHANES II data, those who reported smoking one pack of cigarettes daily had COHb levels up to 5.8% [30]. For every pack of cigarettes smoked per day, the COHb level rises about 2.5% [31]. Rarely, the COHb level in heavy smokers has been reported above 10% [32].

COHb levels in CO-poisoned patients presenting to the ED vary widely because the value depends not only on the circumstances of CO exposure, but also on time since extraction from the exposure and the amount of oxygen administered during that period. Clearance half-time of COHb averages 320 minutes breathing normobaric air, with a range of 128-409 minutes [33]. COHb clearance half-time breathing normobaric 100% oxygen shows significant variation between and within

studies [34]. One credible study performed in actual CO-poisoned patients found an average COHb clearance half-time of 74 minutes [35].

While CO binding to hemoglobin is avid, it is reversible, as evidenced by the clearance half-times noted. Because of delay from termination of CO exposure to COHb measurement and/or interval oxygen administration, a CO-poisoned patient may sometimes have only a mildly elevated or even normal COHb level. A low level does not exclude significant poisoning under the right circumstances.

In data from a nationwide surveillance program on 1,394 patients referred for hyperbaric oxygen treatment of CO poisoning, the average initial COHb level was 23.4 ± 10.4% (range 0.1-77.0%) (36). This is similar to 22.6 ± 11.2% reported in a single institution series of 1,435 patients [37]. It should be pointed that these averages are likely influenced by referral practices, as many hyperbaric facilities use an elevated COHb level, most commonly 20% or 25%, as an independent criterion for treatment [38].

Until recently, no patient has been reported in the English language literature to experience a carboxyhemoglobin level over 70% without demise. In terms of peripheral oxygen delivery alone, it is easy to understand the significance of such a COHb level. If 70% of the circulating hemoglobin is bound with CO and 100% of the remaining hemoglobin sites are filled by oxygen, an arterial oxygen saturation of 30% is the result. For hypoxia to cause this degree of desaturation, the partial pressure of oxygen (PO_2) would be approximately 20 mmHg [39]. Most would readily agree that arterial hypoxia to this degree would soon be associated with cardiac arrest, a condition that has been reported as unsurvivable when caused by CO poisoning [40]. However, a recent report from Turkey in 2016 includes three individuals with COHb levels 71%, 71%, and 73%, respectively, each of whom reportedly survived more than four years after the event [41]. If those COHb levels are correct, survival of those individuals is remarkable [42].

A 2017 report from the Czech Republic described autopsy results from 1,233 deaths related to CO poisoning over 60 years [43]. Mean COHb level among decedents was 66 ± 17% (range 2%-98%). This report is noteworthy in two regards. It supports the clinical impression that COHb 70% is a barrier for survivability. In addition, COHb 98% is the highest level reported in the literature. It is difficult to imagine how the cardiopulmonary system could remain functional long enough to continue CO on-loading and achieve that level.

Carboxyhemoglobin – a marker of exposure

The carboxyhemoglobin complex itself is not known to have inherent toxicity. As such, it should be considered a marker of CO exposure rather than a measure of poisoning severity, except when extremely elevated. Clinical series have consistently found no direct association between presenting COHb levels and patient presentation or symptoms [44,45]. Headache is the most common symptom of CO poisoning. and at least two studies have reported no association between COHb level and severity of headache pain [46,47].

Unless the COHb level is extremely elevated, it should be used as a confirmatory marker of exposure and not a gauge of severity of CO poisoning. The severity of poisoning should be based upon factors that reflect the effect of the poisoning, such as acid-base, neurologic and cardiac status. At first, this seems at odds with the use of a specific COHb level (such as 20%-25%) as an independent criterion for hyperbaric oxygen treatment of CO-poisoned patients. However, those in support of using an absolute COHb level contend that if sophisticated testing were performed, cognitive impairment would be found in almost all patients with COHb greater than 25% [48]. It must be noted, however, that the patient's ultimate outcome is not directly linked to either COHb or physiologic findings such as loss of consciousness. Cognitive sequelae have been shown to occur with similar frequency among those with poisoning of lesser or greater severity, as conventionally graded [49].

CONCLUSIONS

A basic knowledge of COHb is vital to those caring for CO-poisoned patients. With it, the commonly held belief that all patients with CO poisoning are cherry red will hopefully be dispelled, thereby insuring that this myth does not contribute to underdiagnosis of the condition. Understanding measurement techniques is important when interpreting COHb values obtained from different methods. From this follows the recommendation that elevated SpCO levels should be confirmed by laboratory CO-oximetry before making

clinical decisions based on SpCO alone. Knowing COHb levels in different populations and under different conditions allows one to place test results in perspective. Finally, the educated clinician will understand why COHb is a marker of recent exposure to CO and not an indicator of poisoning severity.

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Conflict of interest statement

The author declares that no relevant conflict of interest exists with this submission.

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