Are Reference Intervals for Carboxyhemoglobin Appropriate? A Survey of Boston Area Laboratories

Michael D. Marshall,1 Stephen N. Kales,2,4 David C. Christiani,3 and Rose H. Goldman2

CO is a leading cause of poisoning deaths in the US today. Treating physicians use the carboxyhemoglobin (COHb) % saturation to guide the diagnosis and treatment of CO intoxication. We conducted a telephone survey of hospitals and laboratories in the Boston area, focusing on methodology for COHb determination and accompanying COHb reference intervals. Among 130 facilities, 23 (18%) provide COHb analysis. All facilities that perform the COHb test utilize dedicated multiwavelength photometry. Reference intervals for COHb varied widely among facilities. Eight of 21 (38%) facilities give unacceptably high "normal intervals" for nonsmokers when compared with values available in the literature. Thirteen of 20 (65%) use reference intervals for smokers that are too low, and 3 of 20 (15%) use values that are too high. These reference values provided by the testing facilities may be misleading to the ordering physicians unfamiliar with background COHb saturations. This may lead to misdiagnoses, false reassurances, and perhaps less aggressive treatment than might be warranted. The results of this study argue for wider adoption of COHb reference intervals supported by the current literature.

Indexing Terms: carbon monoxide/CO-oximeters/toxicology

Carbon monoxide (CO) intoxication is a leading cause of poisoning death in the US (1). Sublethal exposure is an important cause of morbidity and leaves some victims with permanent neurologic sequelae (2-4). The diagnosis is confirmed by documenting an increased carboxyhemoglobin (COHb) saturation in either venous or arterial blood.5

Endogenous heme catabolism in the absence of environmental exposure to CO results in ~0.5% COHb (saturating <1% of the body's Hb) (5). Background increases of COHb saturations are most commonly caused by exposure to tobacco smoke and to a lesser extent by air pollution. Most nonsmoking urban dwellers have COHb saturations of <3%, whereas most smokers have chronic saturations of 3-8% (5). Ambient concentrations of CO in urban areas have been reduced since 1975, when the Environmental Protection Agency (EPA) required catalytic converters on all new cars (6).

Low concentrations of CO (enough to produce COHb 2-6%) can decrease exercise time to angina or produce an increase in arrhythmias in nonsmoking patients with known coronary artery disease (7-10). The current Occupational Safety and Health Administration guidelines allow an 8-h time-weighted exposure of 50 μL/L (50 ppm), which corresponds to 6-8% COHb, and the American Conference of Governmental Industrial Hygienists (ACGIH) recommends that an 8-h exposure not exceed an average of 25 μL/L, which correlates with its biologic exposure index (BEI) of 3.5% COHb (11). The EPA standard is 35 μL/L CO for 1 h or 9 μL/L CO as an 8-h mean and is set to maintain <2.0% COHb in the general population (6).

The elimination half-life of COHb is ~4 h when breathing room air and falls to ~1 h when 100% oxygen is given (3). As a result, the COHb obtained on presentation to medical care may be considerably lower than that at peak exposure and may even fall within the "normal range." Therefore, both accurate determination and proper clinical interpretation of COHb saturations <10% are important in ruling out overexposure and avoiding misdiagnosis.

We recently reported an investigation of increased COHb saturations found on routine testing in a group of firefighters (12). Duplicate testing of samples as well as retesting most of the firefighters at a second laboratory by dedicated multiwavelength photometry (CO-oximetry) confirmed that the initial abnormal values were due to inaccurate COHb determination via manual spectrophotometry at the original laboratory.

Another problem with this facility's assay was a minimum detection limit of 4% COHb. This would not be appropriate for occupational assessments, given that the ACGIH BEI allows a maximum COHb of 3.5% in nonsmokers. Also, the reference interval for nonsmokers was ≤5% COHb. COHb saturations ≤5% should not be considered as background for nonsmokers when mean saturation values for smokers of 10-20 cigarettes per day 1 h after the last cigarette have been
reported to be 4.2–5.4%, and most nonsmokers have values much lower (5, 13).

As a follow-up to our experience with this single, large reference facility, we conducted a survey of other hospitals and laboratories in the Boston area, focusing on methodology for COHb determination and accompanying COHb reference intervals.

Methods

All facilities in the 1995 Boston Area Yellow Pages listed under “Laboratories—Medical” and “Hospitals” were eligible for study. A telephone questionnaire survey of each facility was conducted by one of us (M.D.M.). All data were collected in a standard fashion during February 1995. The investigator requested to speak with an individual who was knowledgeable about their laboratories’ methodology for COHb determination.

The facilities were surveyed on information pertaining to the availability of blood testing, testing for COHb, sample requirements, method used for COHb test, reference intervals for COHb provided with results, source for reference intervals, reanalysis for discrepency, machine calibration, and frequency of COHb testing. They were also asked to fax a copy of a sample results form. Comparisons of laboratories with regard to these questions were focused on the methodology, reference intervals, source for these intervals, and information provided to the ordering physician.

Results

A total of 130 facilities were identified and were contacted by phone, 51 under the heading “Laboratories—Medical” and 79 under “Hospitals.” In the laboratory group, 7 (14%) perform COHb analysis; in the hospital group, 16 (20%) test for COHb. The results discussed below refer to the 23 facilities that provide COHb testing.

The laboratory personnel interviewed identified themselves as follows: supervisor, manager, director, or chief technician, n = 13; toxicologist or chemist, n = 1; technician or other laboratory employee, n = 6. All facilities utilize CO-oximetry to measure COHb. A total of five different CO-oximetry models manufactured by three manufacturers are used by the 23 facilities. None of the facilities offers an alternative technique to measure COHb if requested.

Reference intervals for COHb saturations are provided by 21 of 23 facilities. One hospital stated that no normal intervals are available because values must be interpreted on the basis of clinical presentation, and another hospital did not answer this question. Fifteen of the 21 respondents (71%) used different values for nonsmokers and smokers, 5 (24%) give identical values for both nonsmokers and smokers, and a children’s hospital uses a reference interval for nonsmokers only. The reference intervals for both nonsmokers and smokers vary considerably among facilities. The upper limit of normal for nonsmokers ranges from 0.4% to 6.0% COHb. Two of 21 laboratories (10%) give different intervals for urban nonsmokers (≤5% and 6% COHb, respectively), as opposed to rural or suburban dwellers (≤2% and 3% COHb, respectively). The upper limit of normal for smokers ranges from 3.0% to 16% COHb.

Table 1 summarizes the results for reported reference intervals of COHb in nonsmokers and smokers from all responding facilities.

<table>
<thead>
<tr>
<th>COHb est., %, upper limit</th>
<th>Nonsmokers</th>
<th>Smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>10 (43)</td>
<td>—</td>
</tr>
<tr>
<td>2.0</td>
<td>1 (4)</td>
<td>—</td>
</tr>
<tr>
<td>3.0</td>
<td>2 (9)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>5.0</td>
<td>7 (30)</td>
<td>11 (48)</td>
</tr>
<tr>
<td>6.0</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>7.0</td>
<td>—</td>
<td>1 (4)</td>
</tr>
<tr>
<td>9.0</td>
<td>—</td>
<td>1 (4)</td>
</tr>
<tr>
<td>10</td>
<td>—</td>
<td>2 (9)</td>
</tr>
<tr>
<td>12</td>
<td>—</td>
<td>2 (9)</td>
</tr>
<tr>
<td>16</td>
<td>—</td>
<td>1 (4)</td>
</tr>
<tr>
<td>None cited</td>
<td>2 (9)</td>
<td>3 (13)</td>
</tr>
</tbody>
</table>

* For the two facilities reporting different ranges for urban nonsmokers, the higher urban range is the one used in the table.

Table 1. Reported reference intervals for COHb.

Discussion

COHb analysis is provided by 14% of laboratories and 20% of hospitals identified through the Boston Area Yellow Pages. Many of the laboratories listed provide services that do not include blood testing, and many of the hospitals are not acute-care facilities that would diagnose or treat CO poisoning. All facilities that perform the COHb test utilize one of five models of CO-oximeters. These models have been compared with one another and show good reliability among models (14). CO-oximetry results correlate well with gas chro-
matography, the gold standard, at COHb saturations >2.5%, but CO-oximeters discriminate poorly between 0.0% and 2.5% COHb (15). Situations that require detection of COHb <2.5%, e.g., hemolysis research, would ideally be addressed by gas chromatography. No facility offers this method or any other alternative to CO-oximetry. CO-oximetry is a good method for the rapid diagnosis of poisoned patients. In this instance, we are most often concerned with saturations of ≥10% COHb. CO-oximetry is also acceptable for biologic monitoring of occupational and environmentally exposed persons when the expected COHb saturations will be >2.5%.

Despite the use of essentially the same appropriate analytic methods, facilities offered diverse reference intervals that lacked agreement. The upper limits of normal ranged from 0.4% to 6.0% COHb for nonsmokers, and 3.0% to 16% for smokers. No scientific reason is apparent to us for such disparate "normal" values among individuals living in the same metropolitan area whose blood is analyzed by the same technique. It is also inappropriate for five facilities to use the same reference intervals for nonsmokers and smokers when tobacco smoking is the major determinant of background CO exposure in the population. In the second National Health and Nutrition Examination Survey, the 90th percentile for nonsmokers was 1.56% COHb, whereas the 90th percentile for smokers was 1.61% COHb, demonstrating little overlap between the COHb saturation in smokers and nonsmokers (16).

Eight of 21 facilities (38%) classify COHb saturations of 5–6% as normal in nonsmokers. These amounts are too high. In a national survey of blood donors done between 1969 and 1972, the 95th percentile of COHb among nonsmokers was ≤3.0% in 14 of 18 cities, and ≤3.5% in 17 of 18 cities (5). The highest mean and 95th percentile values for nonsmokers were found in Denver and were 2.0% and 3.7% COHb, respectively. Since catalytic converters on automobiles were made mandatory, ambient concentrations of CO have been reduced. For example, in 1976, Denver exceeded the EPA standard on 108 days, but on only 3 days in 1989 (6), and on only 1 day in 1994 (17). Data from the EPA's nine stations in Massachusetts for 1994 revealed no measurements in excess of either the 1- or 8-h standard (17). The EPA standard is set to maintain COHb values in the population at <2.0% saturation. Therefore, we also feel that the use of separate reference intervals for urban nonsmokers of up to 5–6% COHb vs rural nonsmokers is also unwarranted. Saturations >3% COHb in a nonsmoker should always suggest exogenous exposure or cryptic smoking. Such values may be important even in currently asymptomatic patients as indicators of occult exposure from faulty heating units, defective automobile exhaust systems, or vehicles idling outside a building's air intake.

Many of the upper limits of COHb for smokers are also not in agreement with previous studies. Twelve facilities of 20 (60%) use ≤5% COHb as the maximum normals for smokers. In the same national study of blood donors, the median values of COHb among smokers in the 18 cities ranged from 3.2% to 6.2%, and were >5% in 10 of 18 cities (5). Thus, it is not unusual for many smokers to chronically exhibit COHb saturations >5% in the absence of other exposures. Conversely, three facilities (14%) gave excessively high upper limits of normal of 12–16% COHb for smokers. Whereas cigarette smokers can occasionally reach >10% COHb, their values are usually lower. Kahn et al. found the 0–90th percentile for St. Louis smokers to be 0–7.9% COHb (13). Stewart et al. (5) documented 95th percentiles of 7.8–10.4% COHb. We feel that smokers with saturations of COHb ~10% and higher should be carefully questioned regarding other potential sources of CO exposure. Table 2 gives some expected background values for saturation for COHb as reported in the literature as well as those based on occupational and environmental exposure guidelines.

The use of inappropriate reference intervals is probably best explained by evaluation of the reference sources utilized by each facility. Specific textbooks or articles were cited by 71% of laboratories, whereas no hospital cited a specific bibliographic source. Also, 47% of hospitals were uncertain of the source of their values. Furthermore, 45% of facilities stated that their reference intervals came from the operators' manual. When the two US manufacturers were interviewed by telephone, they stated that no reference intervals were provided in their operators' manual.

Five facilities classify certain saturations, 15–25% COHb, as toxic or as requiring treatment, and two of these describe ≥50% COHb as potentially lethal. These values may be misleading to clinicians and lead to a less aggressive approach than what might actually be indicated. The clinical severity of CO poisoning often correlates poorly with the COHb saturation and is determined more by the duration of exposure (3, 23). Severe CO poisoning victims may present with only modest amounts of COHb, and death may occur in a susceptible individual at saturations well below 50%.

Most discussions of CO poisoning warn clinicians about attempting to grade the severity of CO intoxication on the basis of the COHb saturation alone, since neurologic and other toxic effects often do not correlate with the COHb saturation (24).

Some patients may be comatose on arrival with COHb saturations <10–20%, whereas a brief, intense exposure may result in a COHb saturation >50% with minimal symptoms (24, 25). The lack of a close correlation between COHb saturation and poisoning severity relates to differences in individual susceptibilities, acuity/chronicity of exposure, and decays in COHb due to reexposure to fresh air and (or) treatment with oxygen before obtaining the blood sample (3, 20, 26). Only one facility of the 23 performing COHb analysis encourages the ordering physician to interpret the results on the basis of the clinical presentation. This facility gives no reference intervals.

The results of this study can be considered representative regarding laboratory methodology for COHb.
On environmental occupational increases, endogenous CO production increases, and endogenous CO production increases as the rate of minute ventilation and therefore CO uptake on the environment. Thus, under conditions of heavy work, the COHb saturations reached under given CO exposures will increase. Methylene chloride, a chlorinated hydrocarbon solvent, is metabolized to CO in the liver. TLV, threshold limit value; PEL, permissible exposure limit. Adapted from ref. 12.

* As altitude increases, COHb saturations reached from both endogenous exposure and exogenous exposure are expected to increase on the basis of physiologic considerations and animal data. Similarly, as workload increases, so does the rate of minute ventilation and therefore CO uptake on the environment. Thus, under conditions of heavy work, the COHb saturations reached under given CO exposures will increase.

<table>
<thead>
<tr>
<th>Exposure condition</th>
<th>% Hb saturation</th>
<th>Range (percentile of population)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsmokers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Industrial workers</td>
<td>1.38</td>
<td>0.0-2.9 (0-90)</td>
<td>13</td>
</tr>
<tr>
<td>Nonindustrial</td>
<td>0.75</td>
<td>0.0-0.9 (0-90)</td>
<td>13</td>
</tr>
<tr>
<td>Smokers</td>
<td>4.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 µL/L</td>
<td>3.0-4.8</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>1 µL/L</td>
<td>4.7-6.3</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>2 µL/L</td>
<td>4.7-7.7</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Smokers</td>
<td>5.01</td>
<td>0.0-7.9 (0-90)</td>
<td>13</td>
</tr>
<tr>
<td>0.5 µL/L</td>
<td>3.5</td>
<td>3.0-4.0</td>
<td>11</td>
</tr>
<tr>
<td>Industrial workers</td>
<td>4.42</td>
<td>0.0-7.9 (0-90)</td>
<td>13</td>
</tr>
<tr>
<td>Nonindustrial</td>
<td>5.0</td>
<td>1.4-9.1 (0-100)</td>
<td>21</td>
</tr>
<tr>
<td>Smokers</td>
<td>7.0</td>
<td>2.9-13.0 (0-100)</td>
<td>21</td>
</tr>
<tr>
<td>0.5 µL/L</td>
<td>2.0</td>
<td>1.25-2.5</td>
<td>11</td>
</tr>
<tr>
<td>10 µL/L</td>
<td>&lt;2.0</td>
<td></td>
<td>6</td>
</tr>
</tbody>
</table>

Table 2. COHb saturations expected for various conditions and exposures.*

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**Recommendations**

On the basis of the literature, and toxicokinetic and clinical considerations, we propose the following reference intervals: ≤3.0% COHb for nonsmokers, and ≤10% COHb for smokers. The notion that certain threshold COHb saturations define toxicity and potential lethality should be abandoned. Treating physicians should always be warned to interpret all values obtained on the basis of the clinical condition of the patient, including comorbidities, time elapsed since removal from exposure, and prior treatment with oxygen. The possible presence of other toxins such as cyanide in fire victims, and other laboratory data, especially those concerning gas transport and acid-base status, should also be considered. Finally, it should be noted that low or absent COHb saturations do not rule out CO poisoning or exposure with absolute certainty in persons with an appropriate history.

We thank all the facilities who participated in this survey. We are also grateful to Alan Woolf for his thoughtful review of the manuscript. This work was submitted as partial fulfillment of the clerkship requirements in Community Medicine while M.D.M. was a third-year student at Mount Sinai School of Medicine and on a rotation related to R.H.G.’s National Institute of Environmental Health Sciences (NIEHS) award. S.N.K. was supported by the ATSDR Clinical Fellowship in Environmental Medicine. R.H.G. was partially supported by a Public Health Service Environmental/Occupational Medicine Academic Award (1 K07 ES00296–01) from the NIEHS, NIH. D.C.C. was supported by NIEHS Grant Awards ES00002 and ES05947.

**References**

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