

Measurement of Carboxyhemoglobin and Methemoglobin by Pulse Oximetry

A Human Volunteer Study

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Background: A new eight-wavelength pulse oximeter is designed to measure methemoglobin and carboxyhemoglobin, in addition to the usual measurements of hemoglobin oxygen saturation and pulse rate. This study examines this device's ability to measure dyshemoglobins in human volunteers in whom controlled levels of methemoglobin and carboxyhemoglobin are induced.

Methods: Ten volunteers breathed 500 ppm carbon monoxide until their carboxyhemoglobin levels reached 15%, and 10 different volunteers received intravenous sodium nitrite, 300 mg, to induce methemoglobin. All were instrumented with arterial cannulas and six Masimo Rad-57 (Masimo Inc., Irvine, CA) pulse oximeter sensors. Arterial blood was analyzed by three laboratory CO-oximeters, and the resulting carboxyhemoglobin and methemoglobin measurements were compared with the corresponding pulse oximeter readings.

Results: The Rad-57 measured carboxyhemoglobin with an uncertainty of $\pm 2\%$ within the range of 0–15%, and it measured methemoglobin with an uncertainty of 0.5% within the range of 0–12%.

Conclusion: The Masimo Rad-57 is the first commercially available pulse oximeter that can measure methemoglobin and carboxyhemoglobin, and it therefore represents an expansion of our oxygenation monitoring capability.

ALL pulse oximeters in common use measure tissue light transmission at two wavelengths (two colors) to estimate arterial hemoglobin saturation. With only two wavelengths, these pulse oximeters must “assume” the presence of only two light absorbers in the blood: oxyhemoglobin and reduced hemoglobin. If any other light absorbers are present in the blood, the pulse oximeter's calibration may be invalid. Intravenous injection of dyes such as methylene blue can cause very low oxygen saturation (SpO_2) readings—as low as 4% in one study.¹ The common dyshemoglobins, methemoglobin and carboxyhemoglobin, have been shown to produce serious errors in SpO_2 readings in animal studies.^{2,3} These errors have been confirmed in clinical case reports.^{4,5} No previous commercially produced pulse oximeter has suc-

cessfully measured these dyshemoglobins, or even provided accurate SpO_2 values in their presence.

Given the life-threatening dangers of methemoglobin and carboxyhemoglobin toxicity, a pulse oximeter capable of measuring these dyshemoglobins would be an important addition to our monitoring armamentarium. Masimo has now developed such an instrument, the Rainbow-SET Rad-57 Pulse CO-Oximeter (Masimo Inc., Irvine, CA). The Rad-57 uses eight wavelengths of light instead of the usual two and is thereby able to measure more than two species of human hemoglobin. It is approved by the US Food and Drug Administration for the measurement of both carboxyhemoglobin and methemoglobin. In addition to the usual SpO_2 value, the Rad-57 displays SpCO and SpMet, which are the pulse oximeter's estimates of carboxyhemoglobin and methemoglobin percentage levels, respectively.

The current study is aimed at evaluating the accuracy and reliability of the Rad-57 in measuring carboxyhemoglobin and methemoglobin in human volunteers. This is the first human study of a pulse oximeter that claims to detect and measure these dyshemoglobins.

Materials and Methods

Twenty healthy volunteers participated in this study, with informed consent and approval by the institutional review board (University of Arizona Human Subjects Review Committee, Tucson, Arizona). Subjects were divided into two groups of 10 each. One group had carboxyhemoglobinemia induced by inspired carbon monoxide; the other group had methemoglobinemia induced by intravenous infusion of sodium nitrite. Each subject had both peripheral venous and radial arterial cannulas and was monitored by a three-lead electrocardiograph and automated sphygmomanometer. Each subject had Masimo Rad-57 Rainbow sensors on digits 2, 3, and 4 of both hands (six sensors). Blood was sampled periodically from the radial artery cannula (3 ml) for analysis by three calibrated laboratory CO-oximeters: one ABL-730 (Radiometer America, Copenhagen, Denmark) and two Radiometer OSM-3s (Radiometer America). The CO-oximeter analysis provided values of total hemoglobin (grams/deciliter) and percentage levels of oxyhemoglobin, carboxyhemoglobin, and methemoglobin. The last two of these values were compared with the simultaneous readings of the Rad-57 pulse oximeters.

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Group 1: Carboxyhemoglobin

The 10 subjects in the carboxyhemoglobin arm of the study wore a tight-fitting breathing mask connected to a Dräger-2A anesthesia machine (Dräger Medical Division, Lübeck, Germany) *via* a standard circle system. This machine was modified to deliver controlled mixtures of oxygen and nitrogen at any selected fraction of inspired oxygen (F_{IO_2}) to the spontaneously breathing subject. In addition, small amounts of 0.3% (3,000 ppm) carbon monoxide could be introduced into the circle system by flowmeter. After obtaining baseline room air values of vital signs, CO-oximetry readings, and the six pulse oximeter readings, the flowmeters were adjusted to produce an inspired carbon monoxide concentration of 500 ppm. This concentration was monitored by a BW Gas Probe CO Sensor (BW Technologies, Ltd., Calgary, Alberta, Canada), which was located in the Y-piece of the circle system. While the subjects breathed this mixture of 21% oxygen, 79% nitrogen, and 500 ppm carbon monoxide, 3-ml blood samples were aspirated every 10 min from the arterial cannula. These samples were analyzed by the three independent CO-oximeters. The Rad-57 estimates of carboxyhemoglobin percentage, called SpCO, were recorded at the time the blood samples were drawn. When the CO-oximeter carboxyhemoglobin level reached 15%, the inspired carbon monoxide was discontinued, and the F_{IO_2} was changed to 100%. Arterial blood analysis was continued every 10 min until the subject's carboxyhemoglobin level decreased to less than 10%, at which time the mask was removed and the subject breathed room air.

Group 2: Methemoglobin

The 10 subjects in the methemoglobin arm of the study were given an intravenous infusion of sodium nitrite. This drug is approved by the Food and Drug Administration for the treatment for cyanide toxicity.⁶ The usual therapeutic dose is 400 mg intravenously. Sodium nitrite is also a commonly used preservative in processed meats, including frankfurters, bacon, and bologna. Reported side effects of intravenous sodium nitrite include hypotension with rapid infusion, nausea, and vomiting. Accidental overdose can cause cyanosis, headache, weakness, tachycardia, and shortness of breath. In this study, the sodium nitrite was infused at a rate of 6 mg/min to a total dose of 300 mg. The infusion was paused every 10 min for subject assessment, arterial blood sampling, and data acquisition. After completion of the 300-mg infusion, blood gas analysis and data recording were continued until the methemoglobin level had decreased by at least 5% from its peak level.

Statistics

This is a methods comparison study, in which a new method of measuring methemoglobin and carboxyhemoglobin (the Rad-57) is being evaluated for accuracy

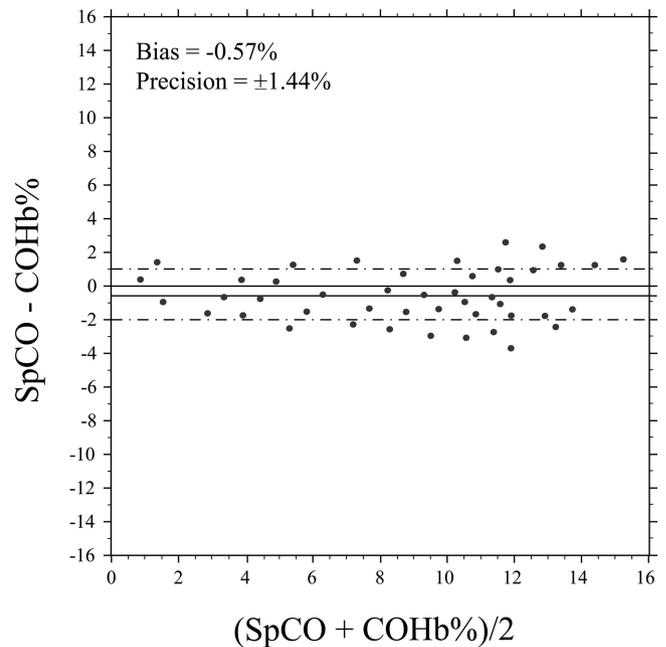


Fig. 1. Bias plot of $(SpCO - COHb\%)$ versus $(SpCO + COHb\%)/2$. Typical single-subject data. SpCO is the Rad-57 measurement of carboxyhemoglobin; COHb% is the average of three CO-oximeters' measurements of carboxyhemoglobin. Lines show values of bias (solid) \pm precision (long/short dash).

and reliability by comparison with an accepted standard method (laboratory CO-oximetry). We have used standard methods comparison statistical techniques. Bias (mean error) and precision (SD of error) were calculated as recommended by Altman and Bland.⁷ Linear regression was used to calculate the slope and intercept of the best fit straight line relation between the two methods. The SE of the estimate was calculated to assess the degree of scatter about the linear regression line. The Pearson correlation coefficient (R) was included for completeness, although this is not the most useful assessment of agreement in methods comparison studies. The correlation coefficient, or R value, is influenced by the range of values covered by the data, as well as by the quality of the agreement.

Results

Carboxyhemoglobin

All 10 subjects reached the planned maximum carboxyhemoglobin level of 15%, and no subject experienced unpleasant symptoms or significant changes in vital signs. After the discontinuation of inspired carbon monoxide, the carboxyhemoglobin levels of all subjects decreased to less than 10% within 1 h.

In the following figures and tables, we define SpCO as the carboxyhemoglobin percentage level measured by Rad-57, and COHb% as the corresponding carboxyhemoglobin level measured by the CO-oximeters. Figure 1 shows a typical single-subject bias plot in which the

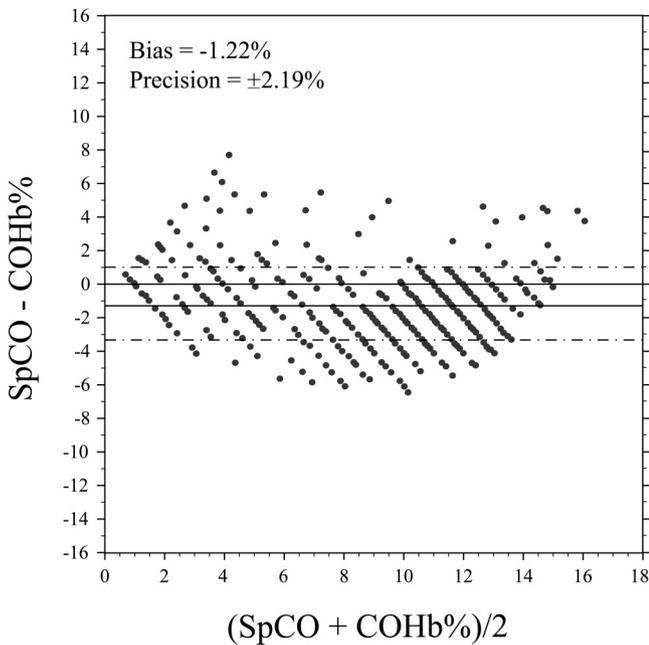


Fig. 2. Bias plot of $(SpCO - COHb\%)$ versus $(SpCO + COHb\%)/2$. Pooled data for 10 subjects. SpCO is the Rad-57 measurement of carboxyhemoglobin; COHb% is the average of three CO-oximeters' measurements of carboxyhemoglobin. Lines show values of bias (solid) \pm precision (long/short dash).

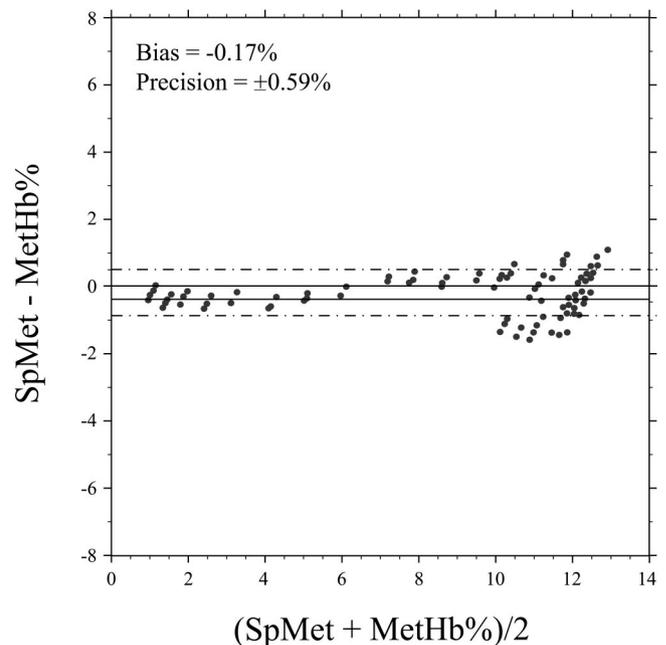


Fig. 3. Bias plot of $(SpMet - MetHb\%)$ versus $(SpMet + MetHb\%)/2$. Typical single-subject data. SpMet is the Rad-57 measurement of methemoglobin; MetHb% is the average of three CO-oximeters' measurements of methemoglobin. Lines show values of bias (solid) \pm precision (long/short dash).

difference between the two methods $(SpCO - COHb\%)$ is plotted versus the mean of the two methods $[(SpCO + COHb\%)/2]$. The plotted CO-oximeter data represent the averages of the readings of the three instruments (one ABL-730 and two OSM-3s). Figure 2 shows the same type of plot for the pooled data of all 10 subjects. Table 1 shows methods comparison statistics for each subject and for the pooled 10-subject data, including bias (mean error), precision (SD of error), linear regression values (slope, intercept, SE of the estimate), and correlation coefficient. The linear regression fit for the pooled data

has a slope of 0.781, a y-intercept of 0.703, and an SE of the estimate of 1.97. The bias is -1.22 , and the precision is 2.19.

Table 1. Methods Comparison Statistics for SpCO versus COHb%, Showing Both Single-subject and Pooled-subject Values

	n	Regression Analysis			Bias	Precision	R
		Slope	y-Intercept	SEE			
Pooled Subject	530	0.781	0.703	1.97	-1.22	2.19	0.867
1	58	0.662	4.773	2.21	2.03	2.76	0.827
2	68	0.890	-0.678	1.62	-1.67	1.70	0.927
3	60	0.839	0.657	1.07	-0.82	1.32	0.966
4	52	0.775	0.294	1.34	-1.70	1.56	0.941
5	40	0.759	-0.537	0.87	-2.63	1.29	0.961
6	56	0.729	0.636	1.70	-1.84	2.08	0.886
7	52	0.904	-1.045	1.89	-1.92	1.91	0.890
8	44	0.710	0.623	0.69	-1.86	1.39	0.974
9	44	0.690	0.613	1.37	-2.11	1.89	0.904
10	56	0.944	-0.085	1.42	-0.57	1.44	0.945

COHb = CO-oximeter measurement of carboxyhemoglobin; n = number of data points for each row of table; R = correlation coefficient; SEE = SE of the estimate; SpCO = Rad-57 measurement of carboxyhemoglobin.

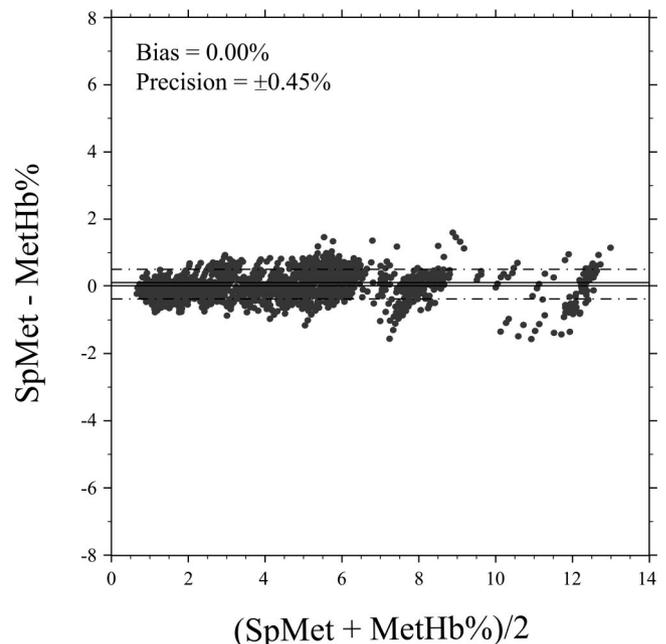


Fig. 4. Bias plot of $(SpMet - MetHb\%)$ versus $(SpMet + MetHb\%)/2$. Pooled data for 10 subjects. SpMet is the Rad-57 measurement of methemoglobin; MetHb% is the average of three CO-oximeters' measurements of methemoglobin. Lines show values of bias (solid) \pm precision (long/short dash).

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Methemoglobin

All 10 subjects completed the entire intravenous infusion of 300 mg sodium nitrite. One subject experienced transient nausea, lasting roughly 2 min. This occurred coincident with a decrease in blood pressure to 90 mmHg systolic. The infusion was halted for 5 min, blood pressure returned to baseline, and the infusion was continued at a slower rate. No other subjects experienced any symptoms. Peak methemoglobin levels ranged from 5% to 12%, and these peaks occurred within 15 min of termination of the sodium nitrite infusion.

Figure 3 shows a single-subject bias plot comparing the Rad-57 methemoglobin reading (SpMet) and the CO-oximeter methemoglobin reading (MetHb%) using the same format as figure 1. Figure 4 shows a similar plot for the pooled 10-subject data. Table 2 shows the methods comparison statistics for pulse oximeter *versus* CO-oximeter methemoglobin readings, in the same format as table 1. The linear regression fit for the pooled methemoglobin data has a slope of 0.999, a y-intercept of -0.004 , and an SE of the estimate of 0.50. The bias is 0.00, and the precision is 0.45.

Discussion

Our results show that the Masimo Rainbow-SET Rad-57 Pulse CO-Oximeter can detect and measure both methemoglobin and carboxyhemoglobin within the ranges covered by this experiment: 0–12% for methemoglobin and 0–15% for carboxyhemoglobin. In assessing the accuracies of the pulse oximeter estimates (SpMet and SpCO), we must also consider the uncertainties of the accepted standard CO-oximeters. The manufacturer's stated uncertainties for both the ABL-730 and OSM-3 are $\pm 0.4\%$ for methemoglobin and $\pm 0.8\%$ for carboxyhemoglobin, within the total hemoglobin range of 7–25 g/dl.

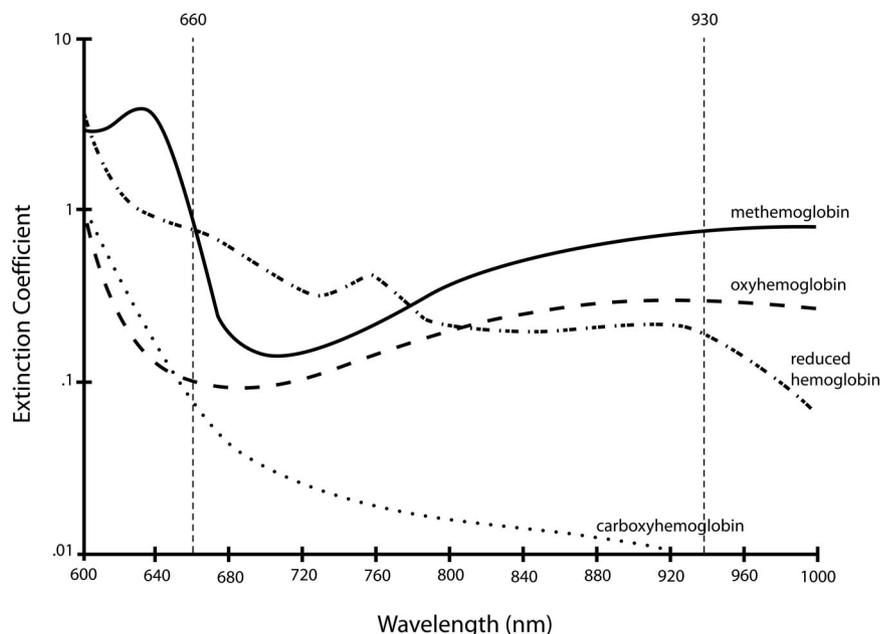
Table 2. Methods Comparison Statistics for SpMet *versus* MetHb%, Showing Both Single-subject and Pooled-subject Values

	n	Regression Analysis			Bias	Precision	R
		Slope	y-Intercept	SEE			
Pooled Subject	970	0.999	-0.004	0.50	0.00	0.45	0.985
1	80	1.109	0.238	0.40	0.17	0.43	0.969
2	70	1.020	-0.043	0.34	0.04	0.34	0.985
3	100	1.080	0.358	0.40	0.09	0.45	0.991
4	80	0.936	0.068	0.78	-0.16	0.78	0.872
5	130	1.008	-0.233	0.59	-0.17	0.59	0.989
6	120	0.971	-0.181	0.40	-0.32	0.41	0.984
7	110	1.030	-0.224	0.24	-0.08	0.25	0.995
8	95	1.103	0.176	0.24	0.52	0.28	0.989
9	90	1.049	-0.140	0.38	0.01	0.38	0.980
10	95	1.117	-0.467	0.23	-0.06	0.29	0.992

MetHb% = CO-oximeter measurement of methemoglobin; n = number of data points for each row of table; SEE = SE of the estimate; SpMet = Rad-57 measurement of methemoglobin; R = correlation coefficient.

Our agreement statistics (bias, precision, linear regression) for the two dyshemoglobin measurements suggests that the Rad-57 has greater accuracy for methemoglobin than for carboxyhemoglobin within the ranges covered by the study. The Bland-Altman precision, which is an indicator of measurement uncertainty, is 2.2% for carboxyhemoglobin and 0.45% for methemoglobin (tables 1 and 2). This uncertainty should be compared with the stated SpO_2 accuracies of current pulse oximeters. Most instruments marketed today specify $\pm 2\%$ uncertainty for SpO_2 values between 70% and 100%, with no specified accuracy for saturations less than 70%. Therefore, the uncertainty for the Rad-57 carboxyhemoglobin measurement found in this study is the same as that specified for

Fig. 5. Light absorbance (extinction coefficient) *versus* wavelength for four hemoglobin species: oxyhemoglobin (O_2Hb), reduced hemoglobin (RHb), methemoglobin (MetHb), and carboxyhemoglobin (COHb). Two wavelengths used by most conventional pulse oximeters (660 nm, 930 nm) are indicated by vertical lines.



conventional pulse oximeters' SpO_2 values. Our measured uncertainty for the Rad-57 measurement of methemoglobin is one fourth that of conventional pulse oximeters; in fact, it is approximately the same as the specified uncertainty of the laboratory CO-oximeters.

This study did not investigate the accuracy of the Rad-57 for the measurement of SpO_2 . The Rad-57 currently uses the same two-wavelength SpO_2 calculation algorithm used by previous Masimo SET pulse oximeters, and the accuracy will therefore be the same as those instruments. Because it calculates SpO_2 using two wavelengths (as opposed to the eight wavelengths used to calculate SpMet and SpCO), the Rad-57 SpO_2 readings will be subject to the usual errors induced by methemoglobin and carboxyhemoglobin, as discussed above.^{2,3}

Since its invention by Aoyagi in 1974, the pulse oximeter has become the most common monitor of patient oxygenation.⁸ However, all pulse oximeters in clinical use to date share a serious limitation. Because they use only two wavelengths of light, conventional pulse oximeters must "assume" that all light absorbances in the arterial blood are caused by reduced hemoglobin (RHb) and oxyhemoglobin (O_2Hb). Under this assumption, these pulse oximeters calculate and display their values of SpO_2 , which are estimates of "functional arterial hemoglobin saturation":

$$Sao_2 = (O_2Hb)/(RHb + O_2Hb). \quad (1)$$

Another important definition is the fractional arterial hemoglobin saturation, given by

$$O_2Hb\% = (O_2Hb)/(RHb + O_2Hb + COHb + MetHb) = (O_2Hb)/(total Hb), \quad (2)$$

where COHb is carboxyhemoglobin and MetHb is methemoglobin. The denominator in fractional saturation includes the amounts of all dyshemoglobins present, whereas in functional saturation they are neglected. In the absence of dyshemoglobins, these two saturations are identical.

Carboxyhemoglobin and methemoglobin both absorb light at the wavelengths generally used by conventional pulse oximeters (fig. 5). The present author (S.J.B.) showed in a 1987 animal experiment that pulse oximeters did not accurately estimate arterial oxygen saturation in the presence of significant levels of carboxyhemoglobin.² Even at carboxyhemoglobin levels as high as 70%, the pulse oximeters displayed an SpO_2 value of roughly 92%. This article concluded that the pulse oximeter "sees" carboxyhemoglobin as though it were composed of approximately 90% oxyhemoglobin and 10% reduced hemoglobin. A later theoretical analysis of the effect of carboxyhemoglobin was consistent with these experimental results.⁹

Carbon monoxide is ubiquitous in our industrial society. It is odorless, tasteless, and extremely toxic. Al-

Table 3. Known Etiologies of Acquired Methemoglobinemia

Medications	
Benzocaine:	used as topical spray for endotracheal intubation, transesophageal echocardiography, esophagogastroduodenoscopy, bronchoscopy; used as topical cream for hemorrhoids or teething preparation
Chloroquine, quinacrine, primaquine:	antimalarials
Dapsone:	antibiotic for Hansen disease (leprosy) and other skin infections
Eutectic mixture of local anesthetics (EMLA):	topical lidocaine, prilocaine
Flutamide	
Lidocaine	
Metoclopramide	
Nitrates	
Nitric oxide	
Nitroglycerin	
Nitroprusside	
Nitrous oxide	
Phenazopyridine (Pyridium)	
Prilocaine	
Riluzole	
Silver nitrate	
Sodium nitrate	
Sulfonamides (sulfasalazine, sulfanilamide, sulfathiazide, sulfapyridine, sulfamethoxazole)	
Medical conditions	
Pediatric gastrointestinal infection and sepsis	
Sepsis	
Recreational drug overdose with amyl nitrate, aka "poppers"	
Sickle cell crisis	
Miscellaneous	
Aniline dyes	
Fume inhalation (automobile exhaust, burning of wood and plastics)	
Herbicides	
Industrial chemicals: nitrobenzene, nitroethane (nail polish, resins, rubber adhesives)	
Pesticides	
Petrol octane booster	

From Ash-Bernal *et al.*¹⁶; adapted with permission.

though 500 ppm is designated by the US Occupational Safety and Health Administration as a maximum "safe" level, this is only for a 15-min exposure. In fact, 500 ppm inspired carbon monoxide will produce lethal levels of carboxyhemoglobin if the exposure is of sufficient duration. The 12 coal miners who recently died in the Sago Mine tragedy were exposed to much higher levels for more than 48 h. Although the Sago accident focused public attention on carbon monoxide poisoning, home and industrial exposures cause numerous deaths and near-deaths every year, resulting in more than 40,000 annual emergency room visits.¹⁰ The generation of carbon monoxide by volatile agents in desiccated Baralyme (Allied Healthcare Products, Inc., St. Louis, MO) has also caused serious toxicity.¹¹

Conventional pulse oximeters also perform poorly in the presence of methemoglobin. This author (S.J.B.) showed in 1989 that high levels of methemoglobin tend to drive the SpO_2 readings toward 85%, no matter what the actual oxygen saturation.³ In this animal study, met-

|| US Department of Labor report on Sago Mine disaster. Available at: <http://www.msha.gov/sagomine/sagomine.asp>. Accessed September 6, 2006.

hemoglobin levels of greater than 60% were produced by intratracheal spray of benzocaine, the local anesthetic found in the topical sprays Cetacaine® (Cetylite Industries, Pennsauken, NJ), Hurricane® (Ada Products, Milwaukee, WI), and Dermoplast® (Prestige Brands, Irvington, NY). The study concluded that in the presence of high methemoglobin levels, the conventional pulse oximeter measures neither fractional nor functional hemoglobin saturation (equations 1 and 2).

There are numerous published case reports of dangerous methemoglobin levels caused by benzocaine and other local anesthetics.^{12,13} Life-threatening methemoglobinemia has also been caused by the antibiotic dapsone¹⁴ and by nitrates or nitrites.¹⁵ The long list of drugs that produce toxic methemoglobin levels is summarized in table 3.¹⁶ Symptoms of methemoglobin toxicity include decreased mental status, headache, fatigue, dizziness, and syncope, followed at higher levels (methemoglobin > 50%) by dysrhythmias, seizures, coma, and death.¹⁶ Acute methemoglobin toxicity is often misdiagnosed, because it can (until now) only be confirmed by laboratory CO-oximetry analysis.¹⁷

The Masimo Rainbow SET Rad-57 seems to be a major advance in pulse oximetry. It is the first commercially produced pulse oximeter to use multiple wavelengths of light, and we have found it to be capable of detecting and measuring both methemoglobin and carboxyhemoglobin. This represents a significant improvement in our oxygenation monitoring capability. Clinical studies are needed to evaluate the performance of the Rad-57 in seriously ill patients and at higher levels of dyshemoglobins.

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