The measurement of carboxyhemoglobin and methemoglobin using a non-invasive pulse CO-oximeter

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A R T I C L E   I N F O
Article history:
Accepted 9 May 2012

Keywords:
Rad-57
Accuracy
Bias
Variability

A B S T R A C T
The pulse CO-oximeter (Rad-57 Masimo Corporation, Irvine, CA) allows non-invasive and instantaneous measurement of carboxyhemoglobin (COHb) and methemoglobin (MetHb) percentage level using a finger probe. However, the accuracy and reliability of the Rad-57 against the gold standard of venous or arterial blood samples have not been clearly established. Thus, the objective of this trial is to evaluate the accuracy and precision of the Rad-57 pulse CO-oximeter by comparing it with venous sampling on the same subjects. Nine healthy subjects were subjected to carbon monoxide such that it raised the COHb to 10–14% on two different days and pooled together. The COHb and MetHb were measured with a blood gas-analyzer and simultaneously with the Rad-57 as the COHb increased from 1.4 to 14%. Results were compared using linear regression and a Bland and Altman method comparison. Mean bias and precision for COHb measured with the Rad-57 was −1% and 2.5%, respectively. The mean bias and precision for MetHb measured with the Rad-57 was 0.0% and 0.3%, respectively. The ability to detect a COHb >10% occurred in 54% of the samples in which COHb was >10–14%. In conclusion, the Rad-57 provides a reading that is between −6% and +4% of the true COHb value for 95% of all samples. The Rad-57 seems to be a good substitute as a first screening test of COHb when the pulse CO-oximeter reads <15%.

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1. Introduction
There are about 50,000 Emergency Department visits for carbon monoxide poisoning per year in the United States (Hampson and Weaver, 2007). The Rainbow-SET Rad-57 pulse CO-oximeter (Masimo Corporation, Irvine, CA) is a new device that allows for a rapid non-invasive determination of the percentage of carboxyhemoglobin (COHb) in blood. The Rad-57 employs eight wavelengths of light. Standard pulse oximeters are composed of two wavelengths and can only measure arterial oxyhemoglobin saturation (SpO₂). This pulse CO-oximeter allows for instantaneous detection of %SaO₂, COHb, and the percentage of methemoglobin (MetHb) in blood. However, the accuracy and precision of this pulse CO-oximeter compared to the gold-standard of multi-wavelength spectrophotometry COHb (Barker et al., 2006; Coulange et al., 2008; Kot et al., 2008; Mottram et al., 2005; Piatkowski et al., 2009; Roth et al., 2011; Suner et al., 2008; Touger et al., 2010). As the results vary from study to study, it was decided to once again evaluate the mean difference (bias) between the two methods (also called accuracy), and precision (SD of the mean difference between methods) of the Rad-57. This research question was timely as we had access to volunteers that were a part of another study that compared the decay of carbon monoxide from blood at various exercise intensities (Zavorsky et al., 2012). As such, these subjects were studied on two different days due to the convenience of accessible volunteers from a concurrent study and not as a deliberate part of the protocol.

This investigation was setup to provide additional evidence on the accuracy and reliability of the Rainbow-SET Rad-57 pulse CO-oximeter to measure the percentage of COHb and MetHb in venous blood. For this purpose, we enrolled healthy volunteers and compared this device with standard blood analysis using multi-wavelength CO-oximeter. The aim of this investigation was to compare the readings from the Rad-57 pulse CO-oximeter to that of blood analysis obtained from a blood-gas analyzer with multi-wavelength CO-oximeter capability, over a COHb varying from 1.4 to 14%. The hypothesis was that the Rad-57 would have a mean bias of around 0% with a precision of 3% compared to multi-wavelength CO-oximeter.
2. Materials and methods

Nine subjects were asked to participate in two separate sessions separated by at least 24 h between sessions. All subjects, healthy volunteers from Marywood University, signed an informed consent form prior to their participation in the study. This study was approved by the Institutional Review Board of Marywood University.

2.1. Methods of measurement

All of the participants were non-smokers and were Caucasian. None of the female subjects participating in the study were wearing nail polish during the days of testing. Each day the same procedure was performed in the same order. A venous line was placed in a peripheral vein near the antecubital fossa on the non-dominant arm for the draw of blood on both days. To prevent the venous line from clotting, a small amount of heparinized saline solution was slowly infused into the peripheral vein. Subjects were sitting upright on a chair at all times of the investigation and stayed still during the measurements. Subjects inhaled, from residual volume, up to total lung capacity, a standard diffusion mixture (0.3% carbon monoxide, 10% helium, 21% oxygen, balance nitrogen), and 40 ppm nitric oxide. Each inhalation lasted for a time frame that ranged from 5 s to 10 s depending on the lung volume of each participant. After every second inhalation, a 2-min rest period followed to stabilize the carbon monoxide percentage in the blood before measurement. Following the 2-min rest period, blood was sampled from a peripheral vein to be analyzed by an arterial-blood-gas analyzer (ABL80 FLEX CO-oximeter, Radiometer America, Copenhagen, DK). The first 5 ml of blood were discarded, and the remaining 1 ml was used as the actual measurement sample. The peripheral vein was flushed after each blood sample with the saline solution containing heparin. Only one blood sample was used for the analysis of COHb and MetHb. If there was an erroneous reading by the blood-gas analyzer, the same syringe of blood was used to obtain measurement. Each blood sample was measured within a maximum of 3 min after the end of the blood draw. Air bubbles were removed from all venous blood samples, and all syringes were shaken to prevent settling or uneven distribution of metabolites prior to being measured by the blood-gas analyzer. At the end of the experiment, patients were either asked to exercise under room air conditions to remove the carbon monoxide, or, to exercise while inhaling 100% oxygen or they were just lying supine under room air conditions. This removal process was part of another study looking at carbon monoxide decay (Zavorsky et al., 2012). The subjects remained in the lab until the COHb reached one-half of the highest recorded level.

2.2. Data collection

At the same time the blood was being drawn from the peripheral vein, the subject had one Masimo Rad-57 Rainbow sensor (Rainbow DCl-dc3) on either digit three or digit four of the non-dominant hand. The digit was chosen according to the appropriate sized sensor for the subject, such that the best finger was positioned in the sensor. The pulse CO-oximeter that measured the COHb and MetHb percentage level in the blood was the Rainbow-SET Rad-57 pulse CO-oximeter (Masimo Inc., Irvine, CA). Both COHb and MetHb level are expressed as a percentage of the total hemoglobin.

The pulse oximeter was placed on the finger each time after the second respiration of the inhalation mixture. The pulse oximeter was left for 1 min to stabilize the COHb and MetHb reading. The data collection of both the COHb and MetHb from the pulse CO-oximeter was accomplished at the end of the blood sampling. Immediately after measurement was recorded, the finger sensor was removed from the finger and the pulse CO-oximeter was turned off. The investigator reported the pulse CO-oximeter values before knowing what the readings were from the blood-gas analyzer. Then subjects inhaled, again, from residual volume, up to total lung capacity, the same inhalation mixture. The pulse CO-oximeter was turned on again, the sensor was placed on the finger for 1 min, and the measurement was repeated. This procedure continued until the COHb reached a maximum of 14%. To reach these maximum percentages in the blood, subjects were required to undergo the CO inhalation procedure about 14–22 times on both days. On another day of the trial, which occurred ≥24 h later, each subject enrolled had a baseline COHb and MetHb <2.5% and 1%, respectively. The primary outcome measures were the percentages of both the COHb and the MetHb measured with the blood-gas analyzer and the pulse CO-oximeter percentages of these same variables.

2.3. Statistical analysis

To assess the accuracy and the precision of the Rad-57 compared to venous blood analysis over two separate days, a Bland and Altman comparison method was used to assess levels of agreement of two different techniques measuring the same parameter (Bland and Altman, 1999). The mean error (bias or accuracy), the standard deviation of the error (precision), and the 95% limits of agreement were calculated. A regression analysis calculating the slope, y-intercept
and the standard error of the estimate (SEE) of the best-fit straight-line relation between COHb obtained from the blood-gas analyzer and the Rad-57 pulse CO-oximeter was also used for method comparison (Hopkins, 2004). A Fisher r-to-z transformation calculated a value of z that was applied to assess the significance of the difference of the two correlation coefficients1 of the regression lines between day one and day two. Finally, a paired t-test was performed to compare the differences between the two methods for determination of COHb and MetHb on day one with differences between the two methods on day two. Data were analyzed using statistical software (PASW Statistics Version 18.0, IBM SPSS Statistics Chicago, IL). p < 0.05 was considered statistically significant.

3. Results

3.1. Subjects

Nine healthy subjects enrolled (age = 23 ± 4 years, body mass index = 23 ± 3 kg/m²) were initially a part of another study (Zavorsky et al., 2012). We took advantage by accessing these same subjects to examine the precision and accuracy of the Rad-57. On the first day of the experiment, the COHb reached a maximum of 13.9% in one case, and MetHb to 1.3% on a few cases. On the second day of the experiment, seven subjects remained. Two subjects did not participate on the second day of the investigation, as they decided not to partake in further venous blood withdrawals of which they were a part of another study examining the effect of exercise on CO removal from blood. None of the participants encountered complications. During the investigation, all vital signs were stable and participants denied any complaint of unpleasant symptoms or side effects. No erroneous readings by the blood-gas analyzer were recorded. All the subjects enrolled left the laboratory the same day of the trial when the COHb reached one-half of the highest recorded level, which was within a maximum of 6 h for all participants. The COHb and MetHb were defined as the corresponding carboxyhemoglobin and methemoglobin percentages in venous blood measured by the blood-gas analyzer, respectively. The COHb and MetHb percentages measured by Rad-57 were defined as SpCO and SpMet, respectively.

3.2. Main results

The mean bias and precision of predicting COHb from SpCO were nearly identical for both days. There was no significant difference between two different correlation coefficients of the regression lines between day one and day two (two-tailed z-statistic = 1.269, p = 0.205). There was also no difference between the two methods on day one versus day two (paired t-test t-statistic = −0.216, p = 0.083). Thus, the data were pooled. The COHb measurements ranged from 1.4 to 13.9% between the two days. The mean bias (SpCO–COHb) was −0.8% and the precision was 2.5% [95% CI of the mean bias was −1.21 to −0.4%]. That is, the Rad-57 provides a reading that is between −6% and +4% of the true COHb value for 95% of all cases, so that if the Rad-57 reads 10%, the COHb will be between 4 and 14%. The paired t-test between SpCO and COHb was significant (paired t-test t-statistic = −4.06, df = 147, p = 0.000).

The MetHb measurements ranged from 0.1 to 1.3% between the two days. The mean bias and precision of predicting MetHb from SpMet were nearly identical for both days. There was no significant difference between two different correlation coefficients of the regression lines between day one and day two (two-tailed z-statistic = −0.4, p = 0.689), nor were the correlation coefficients of the regression lines significant. As such, there was no significant relation between MetHb and SpMet on either day one or day two. Furthermore, there was no difference between the two methods on day one versus day two (paired t-test t-statistic = 1.17, df = 147, p = 0.245), thus allowing all the data to be pooled together. The mean bias (SpMet–MetHb) was 0.0% and the precision was 0.3% [95% CI of the mean bias was −0.1 to 0.0%].

We also determined the sensitivity and specificity of the CO-oximeter. At COHb values ≥10% to 14%, the Rad-57 CO-oximeter had a sensitivity of 54%, meaning that the CO-oximeter correctly identified 13 of the 24 measurements that had a COHb value ranging from ≥10% to the highest value of 14%. The specificity was 89%, meaning that the CO-oximeter correctly identified 110 measurements (out of 124) with COHb below <10%. As such, the false positive rate (false alarm) was 11% (14 samples) and the false negative rate (false miss) rate was 46% (11 samples).

4. Discussion

4.1. Novelty of this trial

The purpose of this investigation was to examine the mean bias and precision of the Rad-57 pulse CO-oximeter compared to the gold standard of venous blood samples measured by multi-wavelength CO-oximetry. As mentioned previously, the primary reason that the subjects were studied on different days was due to the convenience of accessible volunteers from a concurrent study and not as a deliberate part of the protocol.

The differences between the two measurements were consistent for both parameters on the same subjects over both days. That is, the errors comparing the two methods of measurement were the same for both COHb and MetHb on day one and on day two (as would be expected). The accuracy and the precision of the Rad-57 has been validated by Barker et al., 2006; Cou Lange et al., 2008; Kot et al., 2008; Mottram et al., 2005; Piatkowski et al., 2009; Roth et al., 2011; Suner et al., 2008; Touger et al., 2010), however, due to the varied results between studies, it was decided that further research was needed. The present study demonstrates that the Rad-57 provides coherent and reproducible day-to-day measurement of COHb and MetHb in the same conditions, starting with the same baseline values each time.

4.2. Main findings: COHb

The manufacturer of the Rad-57 notes an accuracy of ±3% when the COHb is from 1% to 40%. Others have determined that the accuracy (mean bias) can be −4.2% (Suner et al., 2008) to 3.2% (Piatkowski et al., 2009). In this study, we found the accuracy to be about −0.8%, rounding up to 1% (since the Rad-57 reports SpCO in whole units). That is, on average, the device underestimates the COHb by 1%.

The precision of ±2.5% that we obtained for SpCO is consistent with other findings (Barker et al., 2006; Coulange et al., 2008; Piatkowski et al., 2009). The precision is probably a better indicator of the performance of the Rad-57 as the precision provides the standard deviation of the error of the unit. A recent study (Barker et al., 2006) conducted in a laboratory on 10 volunteers found similar results for SpCO (mean bias = −1.2%, precision = ±2.2%), with an almost similar range of COHb, 0–15%. Our results are also in agreement with the precision obtained in emergency department patients. In fact, out of 1578 subjects enrolled, 17 were diagnosed with carbon monoxide intoxication (precision = ±3.3%) (Roth et al., 2011). In contrast, Touger et al. demonstrated a precision of ±6.6% in the emergency department leading the authors to claim that the Rad-57 cannot replace standard laboratory blood-gas

1 The correlation coefficient measures the strength of a relation between two variables, not the agreement between them.
analysis (Touger et al., 2010). However, this statement is made on the a priori assumption that a precision of ±5% COHb is clinically significant. About 24 out of 120 subjects had a COHb ≥ 15% (Touger et al., 2010). As with Touger, others found the precision to be quite poor at ±4.3% (Kot et al., 2008). Both the mean bias and precision then allows for the limits of agreement of the unit to be defined. We determined that the Rad-57 underestimates COHb on average by 1%. This means that 95% of the time COHb is as much as 4% above the SpCO or as much as 6% below the SpCO. So, if the real value for COHb is 10%, the SpCO, on average, will read 9%, and thus the 95% limits of agreement will be between 3 and 13%. The Rad-57 seems to be a useful device as a first screening test to determine whether an intoxication occurred. However, it is not precise enough in a research setting to determine low COHb value (i.e. below 15%).

The sensitivity observed in this study was 54%. That is, the ability to detect a true raised COHb occurred in half of the samples in which COHb was ≥ 10–14%. Touger et al. (2010) reported nearly the same sensitivity, although their lower cut-off was a COHb of 15%. In light of this low sensitivity, it has been advocated that the Rad-57 cannot be used to exclude carbon monoxide poisoning in any patient with an appreciable risk of being intoxicated (Maiser and Lewis, 2010). However, since the specificity was 89%, similar to the data from Touger et al. (2010), there is clinical utility for screening of patients to avoid a large number of false-positive tests and also to use it as a first screening on patient with no symptoms with potential carbon monoxide intoxication. When a reading of SpCO ≥ 15% is read by the CO-oximeter a second invasive screening with blood drawing should be performed to ensure whether carbon monoxide intoxication occurred.

It has been suggested that patients with a COHb of 25% or more should undergo hyperbaric oxygenation regardless of the presence of symptoms (Kao and Nanagas, 2005). This is consistent with reviews and meta-analyses, which state the heart and brain become severely affected when COHb in the blood surpasses 20% (Procop and Chichkova, 2007; Benignus et al., 1990; Benignus, 1994). Since the presence of symptoms secondary to an exposure to carbon monoxide intoxication is not directly proportional to the percentage of COHb in the blood, all patients with a suspected carbon monoxide poisoning should undergo a monitoring of their dehemoglobinins, even if they do not present any symptoms in order to decide whether an appropriate treatment is necessary. However, based on the data obtained in this study, the Rad-57 should probably be used as a first screening until a reading of SpCO ≥ 15% is obtained. The advantage of this first screening is its non-invasiveness and rapid reading. Thus Rad-57 should be used as a first screening to determine whether an invasive blood measurement of COHb should be performed to confirm the intoxication.

4.3. Main findings: MetHb

Methemoglobin can be formed through direct or indirect oxidizers that react with hemoglobin. Independently of its formation, the severity of symptoms related to agents that oxidize hemoglobin is proportional to the MetHb. Thus, MetHb is directly related to the percentage of total hemoglobin (Wright et al., 1999). Consequently, MetHb might not be correlated with symptoms in some cases. In general, neurologic and cardiovascular symptoms (dizziness, headache, anxiety, dyspnea, drowsiness, and seizures) are commonly present with MetHb above 20–30% (do Nascimento et al., 2008). We had subjects inspire 40 ppm of nitric oxide to total lung capacity for 14–22 different inspiration maneuvers to raise MetHb, however, there was minimal increases in MetHb. Thus, the results on MetHb may not be informative enough to draw interpretations.

Nevertheless, when MetHb is below 1.3%, the Rad-57 can measure MetHb in the blood such that the true value will range from ±0.7% for 95% of all cases, similar to other reports (Barker et al., 2006). Thus, if the Rad-57 reads 1% for SpMet, the MetHb will be between 0.3% and 1.7% for 95% of all cases.

4.4. Limitations

There are some limitations in this study. First, measurements of both COHb and MetHb were collected based on the maximum COHb reached and not MetHb. The measurements of MetHb were collected independently from the maximum percentage reached in the blood, because the target aimed to record data was the level of COHb. The addition of 40 ppm nitric oxide to every inhalation maneuver did not sufficiently raise MetHb above 1%, with the exception of a few samples. Second, both COHbs and MetHbs were measured with the blood-gas analyzer using venous blood and not arterial blood. However, a venous line is easier to insert and less painful compared to an arterial line. Venous samples also show agreement compared to arterial samples for measurement of COHb (Touger et al., 1995; Turner, 2000). Third, we used a small sample of healthy subjects. The trial has been conducted in a laboratory and not in a hospital, which might limit generalization our findings. In addition, O’Malley and colleagues advocated the possibility that skin pigmentation might influence the reading of the pulse oximeter (O’Malley, 2006). Since the present trial enrolled only Caucasian subjects, our findings cannot be applied to all skin pigmentation types. Finally, for safety measures, the maximum COHb reached was 14%; and this percentage was reached only in one case. Thus, the error of the CO-oximeter reading when COHb is ≥ 14% could only be speculated to be the same.

5. Conclusion

The RAD-57 provides a reading that is between –6% and +4% of the true COHb value for 95% of all samples. Rad-57 appears to be a useful rapid and non-invasive method for initial screening of the patients arriving to the emergency department with suspected carbon monoxide intoxication. However, when the readings of SpCO are ≥ 15% with Rad-57 a second screening with blood drawing should be performed to ascertain carbon monoxide poisoning.

References
