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EMERGENCY DEPARTMENT MANAGEMENT OF SUSPECTED CARBON MONOXIDE POISONING: ROLE OF PULSE CO-OXIMETRY

Running title: detection of CO-poisoning using SpCO in the ED

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ABSTRACT (280 words)

Study objective: The RAD-57 pulse CO-oximeter is a lightweight device allowing non-invasive measurement of blood carboxyhemoglobin (SpCO).

We assessed the diagnostic value of pulse CO-oximetry, comparing SpCO to standard laboratory blood measurement (COHb) in emergency department (ED) patients with suspected carbon monoxide (CO) poisoning.

Methods: This was a prospective, diagnostic accuracy study according to STARD criteria (Standards for the Reporting of Diagnostic accuracy studies) in consecutive adult ED patients with suspected CO poisoning. Transcutaneous SpCO was obtained using the RAD-57 simultaneously with blood sampling for laboratory blood gas analysis, with no change to standard management of CO poisoning. Correlation between SpCO and COHb was assessed using Bland and Altman's method. Diagnostic performances of SpCO for the screening of CO poisoning were determined using ROC curve analysis. Blood COHb levels >5% and 10% for non-smokers and smokers respectively were applied as the reference standard.

Results: 93 patients were included (56 smokers, 37 non-smokers). CO poisoning was diagnosed in 26 patients (28%). SpCO values ranged from 1% to 30%, with a median of 4% (IQR: 2.7 - 7.3). COHb values ranged from 0% to 34%, median: 5% (IQR: 2 - 9). Mean differences between COHb and SpCO values was -0.2% ± 3.3%, with 95% limits of agreement (LOA) [-6.7%, +6.3%] COHb (-0.7%, LOA [-7.7, +6.2] for non-smokers ; +0.6%, LOA [-5.0, +6.2] for smokers). 6% and 9% SpCO provided optimal thresholds for detecting CO poisoning, in smokers and non-smokers respectively.

Conclusion: SpCO measurement using the RAD-57 pulse-oximeter cannot be used as a substitute for standard blood COHb measurement. However, non invasive pulse CO-oximetry could be useful as a first-line screening test, enabling rapid detection and management of CO-poisoned patients in the ED.

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INTRODUCTION

Background

Carbon monoxide (CO) poisoning represents the main cause of death by poisoning in Europe and in the United States (1, 2). In France, approximately 6000 patients are treated annually for suspected or confirmed CO exposure, of whom 2500 are admitted to hospital and 300 die (3). Due to potential severity and the necessity of immediate therapy, there is an urgent need for both rapid and reliable screening and management of CO poisoning (4, 5). However, clinical signs are polymorphic and unspecific. They vary in time and from one patient to another (6, 7). The diagnosis of carbon monoxide intoxication remains a challenge to clinicians, especially in the context of occult CO poisoning, in the absence of specific symptoms or an evocative context (fire, failing heating systems, unhealthy housing environment, presence of other victims, including animals).

Besides clinical signs and circumstances, the diagnosis of CO poisoning relies on the blood carboxyhemoglobin (COHb) levels, from venous or arterial blood gas analysis (8).

A lightweight pulse CO-oximeter enabling non invasive CO measurement (SpCO) through a fingertip sensor has been approved for use in clinical practice since 2005 (RAD-57, Masimo Inc., Irvine, CA).

However, clinical data supporting the use of non invasive pulse CO-oximetry in patients with suspected CO poisoning in the actual clinical context is still sparse. Most published studies evaluated population-based screening or small population of patients with suspected CO poisoning, with relatively low levels or range of CO exposure, and results from accurate comparisons between RAD-57 measurements and laboratory blood gas analysis in emergency department (ED) patients suspected of CO poisoning are still being debated (9).

The first preliminary data to evaluate the use of the RAD-57 in ED patients with CO

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poisoning showed good agreement, when compared with laboratory blood gas analysis (10). This was further confirmed in 64 ED patients, regardless of the cause of admission to the ED (11). Acceptable difference between the two methods of measurement was also reported in other clinical settings involving small numbers of poisoned patients with high COHb levels, including both a hyperbaric center and a burn unit (12, 13).

However, three recent and better powered ED studies have shown different findings. Either poor or acceptable concordance between the two methods of measurement was reported; reliability of the RAD-57 device in detecting CO poisoning was advocated in one study (14-16). Acceptable agreement and reliability of this device to measure blood COHb have been reported in laboratory studies involving human volunteers (17, 18). This raises the need for more clinical test data evaluating the role of pulse CO-oximetry in real ED conditions.

Rapid and non invasive detection of elevated blood COHb levels could improve diagnosis and subsequent management of acute carbon monoxide poisoning in emergency medicine.

Further evaluation of the performance of the RAD-57 pulse CO-oximeter and its possible use as a screening tool in ED conditions is needed.

The aim of our study was to evaluate the reliability and accuracy of the RAD-57 pulse CO-oximeter as a screening tool for acute CO poisoning in ED patients with suspected CO poisoning.

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MATERIALS AND METHODS

Study design and Setting

This was a prospective, diagnostic accuracy study according to STARD criteria (Standards for the Reporting of Diagnostic accuracy studies). Study was conducted in an urban-based University Hospital ED, with a census of 50,000 visits per year. Consecutive adult patients presenting with suspected CO poisoning were included over a 19 month-period. Transcutaneous SpCO was measured using the RAD-57 pulse CO-oximeter, simultaneously with standard venous blood sample for laboratory blood gas analysis, with no change to standard carbon monoxide poisoning management. The two methods of carboxyhemoglobin measurement were compared. The study was approved by the local ethics committee, with a waiver of written informed consent.

Selection of participants and interventions

Participants were consecutive patients, aged 18 years or older, admitted to the ED for suspected CO exposure. Diagnosis of CO intoxication was evoked according to clinical symptoms or circumstances. After a complete physical examination, patients were tested using the non-invasive RAD-57 pulse CO-oximeter. Venous blood was sampled for standard laboratory carboxyhemoglobin measurement, according to standard ED management procedures for CO poisoning. Blood sampling and RAD-57 measurement were to be performed simultaneously. The following data was prospectively collected: reason for admission, age, gender, physiologic variables, smoking habits, heart rate, systolic and diastolic blood pressure, SpO2, SpCO, standard laboratory test results including blood COHb, and electrocardiography. Timing of both blood sampling and RAD-57 measurements was also recorded. Data was entered into an Excel database for further analysis (Microsoft

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Corporation, Redmond, WA).

Methods of measurement

Pulse CO-oximetry

Non invasive pulse CO-oximetry was carried out by nursing staff already trained in the use of the Rad-57 pulse CO-oximeter (Masimo, Inc., Irvine, CA, USA). SpCO measurement was performed using the adult sized sensor (Sensor, Rev. B) placed on the 3rd or 4th digit, according to manufacturer recommendations. Nail polish was removed if necessary. SpCO was expressed in total percentage of hemoglobin.

Standard blood gas analysis

Venous blood was collected into EDTA treated tubes (Beckton Dickinson) and sent to the toxicology laboratory for further carboxyhemoglobin testing. Blood carboxyhemoglobin was analyzed by derivative spectrophotometry using an automated CO-oximeter (IL 682, Instrumentation Laboratory SpA V.le Monza 338-20128 Milan, Italy). Blood carboxyhemoglobin was detected within a range of 0-100% and accuracy of ± 0.5% and reported as percentage of total haemoglobin.

Outcome Measures

Blood carboxyhemoglobin levels measured transcutaneously using the RAD-57 pulse CO-oximeter or by standard laboratory blood tests from venous blood samples.

Diagnosis of CO poisoning was confirmed when laboratory COHb values were strictly greater than 5% and 10% for non-smokers and smokers respectively (4).

Primary Data Analysis

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Descriptive statistics were used to describe the variables, including mean, standard deviation (SD), median and ranges. Time interval between RAD-57 measurements and blood sampling was calculated as COHb time (h:mn) - SpCO time (h:mn) and reported as an absolute value. Correlation between SpCO and COHb was tested using intraclass correlation coefficient, along with 95% confidence intervals (CI), based on Fisher's transformation. Agreement between the two methods of measurement was assessed according to Bland and Altman (19). Differences between measurements were calculated as COHb - SpCO. Mean (SD) and ranges were calculated for the differences between measurements to provide measures of bias and imprecision. Upper and lower limits of agreement were calculated as the mean difference ± 1.96 SD.

The overall diagnostic value of SpCO was quantified by calculating the area under the ROC curve (AUC) using the trapezoidal method, with 95% CI. SpCO thresholds for the identification of CO poisoning were calculated using ROC curve analysis, based on normal COHb cut-offs (5% in non-smokers and 10% in smokers). Optimal thresholds for the best combined sensitivity and specificity were determined using the Youden index. Diagnostic parameters (sensitivity, specificity, and predictive values) were calculated for each SpCO threshold, along with 95% CI, based on normal approximation. The significance level was set at $p \leq .05$ for all tests. Statistical analysis was performed by GM at the Department of Medical Information with SAS software version 9 (SAS Institute, Cary, NC).

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RESULTS

Characteristics of Study Patients

During the 19 month study, 95 patients with suspected CO poisoning were eligible for inclusion, 2 patients were excluded for missing data and 93 patients were included. Patient characteristics are shown in Table 1.

A diagnosis of CO-poisoning was retained for 26 patients (28%), including 21 non-smokers and 5 smokers, based on widely accepted 5% and 10% COHb thresholds for non-smokers and smokers respectively. Median COHb levels were 7.8 % [IQR 6.6 -11.8 %] and 12.0 % [IQR 10.8 – 15.5 %] in non smokers and smokers, respectively.

Agreement between COHb and SpCO

RAD-57 measurements and blood sampling for laboratory COHb determination were performed within a span of 19 min (95% CI: 10-29 min). RAD-57 measurement and blood sampling were performed simultaneously in 33% of cases. SpCO was tested before blood sampling in 46% of cases.

Distribution of SpCO values ranged from 1% to 30%. Distribution of COHb values ranged from 0% to 34%. Median values are shown in Table 1.

Moderate correlation was found between the two methods of measurement r = 0.7 (95%CI: 0.58 - 0.79) (Figure 1).

Agreement between SpCO and COHb measurements was assessed using the Bland and Altman method. Mean bias (COHb - SpCO) and precision were -0.2% (95% CI -0.44 to +0.02 %) (SD 3.3%), with limits of agreement of -6.7% and +6.3% for the entire cohort (Figure 2A).

Mean bias and precision were -0.7 % (95% CI: -1.04 to -0.41) (3.6 %) for non-smokers, with

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limits of agreement of -7.7% and + 6.2% (Figure 2B). Mean bias and precision were 0.6 % (95% CI: -0.34 to +1.48) (2.8 %) for smokers, with limits of agreement of -5.0% and + 6.2% (Figure 2C).

Diagnostic performance of SpCO

ROC curves were used to identify SpCO thresholds, enabling discrimination between poisoned and non-poisoned patients, with the best combined sensitivity and specificity.

Area under the ROC curve was 0.84 (95% CI: 0.74 to 0.94) in the entire patient cohort.

An SpCO of 9% provided the optimal threshold for detecting patients with COHb levels greater than 10% in the entire patient cohort.

Area under the ROC curve of SpCO was 0.83 (95% CI: 0.71-0.95) for non-smokers and 0.98 (95% CI: 0.89 -1) for smokers.

Optimal SpCO threshold was 6% for non-smokers (Figure 3A) and 9% for smokers (Figure 3B). Performance characteristics for each SpCO threshold are shown in Table 2.

Seven false negatives were found.

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DISCUSSION

Our results confirm that SpCO measurement using the RAD57 pulse-oximeter cannot be used as a substitute for standard blood COHb measurement in ED patients with suspected CO poisoning. However, our results, obtained in real ED conditions, also show that non invasive pulse CO-oximetry allows rapid detection of CO-poisoned patients, among ED patients with suspected CO poisoning.

We found SpCO, with a bias of -0.2%, to slightly underestimate blood COHb levels in our entire ED patient cohort. However, SpCO tended to overestimate COHb in smokers, with a bias of 0.6%. The precision of the RAD-57 measurements was 3.3% in our study cohort, which closely matches the measurement precision claimed by the manufacturer (3%), supporting the reliability of the non invasive RAD-57 in actual ED conditions.

We report limits of agreement between pulse SpCO and blood COHb of -6.7% to +6.3%.

These limits are similar to most limits of agreement previously reported in the literature, whether in the ED setting, in other in-hospital conditions (such as Burn Center, Hyperbaric Center Respiratory Department) or in healthy volunteers subjected to CO (10-12, 17, 18).

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Bland and Altman analysis shows that the higher the value of COHb, the more pulse CO-oximetry tends to overestimate COHb value.

We found 6 patients (6%) with COHb levels higher than 15% in our ED patient cohort. The accuracy and reliability of SpCO for detecting high levels of COHb (COHb>15%) has been explored in a physiological study, including 10 healthy volunteers under experimental conditions. A good correlation was found, with limits of agreement ranging from -5.5% to 3.1%, a bias +1.2% and an accuracy of ± 2.2%, close to that we found in ED patients with suspected CO poisoning, further supporting our findings (17).

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Multiple factors may influence the discrepancy between pulse SpCO and blood COHb measurements. Besides SpCO value, smoking, age and time interval between measurements have been identified as independent influencing factors (15). Methemoglobin, body temperature, and blood pressure may also influence the SpCO accuracy (16). Additionally, factors related to the use of the RAD-57 device may alter SpCO measurement, including an incorrectly positioned fingertip sensor, or the presence of false nails, nail polish or a dye such as henna on the nails and fingertips.

Nonetheless, our study shows that pulse CO-oximetry may be an effective tool in detecting CO-poisoning in patients with suspected CO poisoning, in real ED conditions, and with an acceptable level of accuracy.

Using commonly accepted blood carboxyhemoglobin thresholds for the diagnosis of CO poisoning (ie COHb levels greater than 10% and 5% in smokers and non-smokers respectively), our study identified two SpCO thresholds, that can be used to distinguish CO poisoned patients from non-poisoned ones, with good sensitivity, specificity and predictive values, when considering the patient's smoking status (SpCO threshold $\geq$ 9% for smokers, $\geq$ 6% for non-smokers). The optimal SpCO threshold derived from our ED patient cohort (9 %) is slightly higher than that reported by Roth et al (15). They report an upper limit of normal cut-off of 6.6% SpCO in a large screening for occult CO poisoning in the ED. Their analysis was based on a limited number of patients with a diagnosis of CO poisoning, and normal COHb cut-off used for confirming the diagnosis of CO poisoning was not disclosed.

Furthermore, our findings support the possibility of developing an algorithm for sorting and prioritizing patients with suspected CO poisoning upon arrival at the ED. Risk stratification

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could then be based on pulse CO-oximetry result and patient smoking status. Patients with suspected CO poisoning and first line positive RAD-57 testing (SpCO ≥ 9% for smokers, ≥ 6% for non-smokers) could benefit from immediate care. However, a negative RAD-57 testing will not exclude standard blood carboxyhemoglobin measurement to confirm CO poisoning.

A feature of CO poisoning is its collective nature. Rapid detection and prioritizing of patients suspected of CO poisoning could prove crucial in the ED, allowing real time optimization by implementing a management strategy including detection, prioritizing and care. More rapid diagnosis and initiation of hyperbaric oxygen therapy in CO poisoned patients evaluated by pulse CO-oximetry compared with laboratory CO-oximetry has been recently shown in a retrospective study (20). Further studies are needed to optimizing the diagnostic value of pulse CO-oximetry according to the clinical setting, especially for the pre-hospital screening.

LIMITATIONS

The study was conducted in a single center. Results may not be directly extrapolated to other patient populations and clinical settings, including in-hospital conditions.

Carboxyhemoglobin measurements were performed upon admission to the ED, following carbon monoxide exposure. There was a 19 min median time interval between blood sampling and SpCO measurement. This time interval remained below the COHb half-life, even for patients treated with normobaric 100% oxygen, with a limited systematic bias regarding timing of either measurement. The time-lapse from the end of CO exposure, as well as the possible oxygen therapy provided by pre-hospital emergency services, prior to ED management, may explain the relatively low values of COHb recorded in the entire patient cohort. Nevertheless, this reflects real ED conditions, with patients presenting to the ED after varying degrees of time lapses from the end of CO exposure. 28% of the patient cohort was

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diagnosed with CO poisoning, based on COHb thresholds (COHb > 10% and COHb > 5% for smokers and non-smokers, respectively). Few patients presented with high (COHb > 15%) or very high (> 25%) COHb levels.

Delays from the end of CO exposure to ED admission, as well as use and duration of oxygen therapy were not recorded.

Methemoglobinemia, which could also be a source of error in the detection of COHb levels, was not assessed.

CONCLUSION

SpCO measurement using the RAD-57 pulse-oximeter cannot be used as a substitute for standard blood COHb measurement in ED patients with suspected CO poisoning.

However, non invasive pulse CO-oximetry could be useful as a first-line screening test, enabling rapid detection and management of CO-poisoned patients in the ED.

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Abbreviations:

CO, carbon monoxide; COHb, carboxyhemoglobin; SpCO, carboxyhemoglobin determined by pulse oximetry; ED, emergency department; SD, standard deviation

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FIGURE LEGENDS

Figure 1. Scatter plot showing the relationship between pulse carboxyhemoglobin values (SpCO, %) measured using the RAD57 pulse CO-oximeter and standard carboxyhemoglobin values (COHb, %) obtained from laboratory blood gas analysis.

N=93. Correlation coefficient is r=0.66 (95% confidence interval 0.91 - 0.97). Linear regression relationship is y = 0.75 x + 1.74 as shown by the solid line.

Figure 2. Bland and Altmann graphs showing the difference between transcutaneous pulse CO-oximetry (SpCO, %) and standard carboxyhemoglobin laboratory measurement (COHb, %) plotted against the average of measurements. Horizontal lines represent the mean bias (broken line), and upper and lower limits of agreement (LOA) (dotted lines). A. All patients, mean bias = -0.21 %, LOA – 6.7 % and + 6.3 %. B. Non smokers. N=56, mean bias = -0.7, and LOA -7.7 and + 6.2 %, and C. Smokers. N=37, mean bias=0.57, and LOA -5.0 and + 6.2 %.

Figure 3. ROC curves showing optimum SpCO cutoffs for screening CO-poisoned patients. A. Non-smokers N=56. B. Smokers N=37.

Blood COHb levels COHb> 5% and COHb> 10% were used as reference standard for the diagnosis of CO poisoning in non-smokers and smokers, respectively.

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Table 1. Patient Characteristics

Characteristics	Value
Age, y	43 (20) range (18-92)
Gender Male/Female	42 (45 %) / 51 (55 %)
Smoking status	
smoker	37 (40 %)
non-Smoker	56 (60 %)
Type of CO exposure	
domestic causes	37 (40 %)
smoke Inhalation	53 (57 %)
other	3 (3 %)
Blood COHb levels (%)	4 (IQR: 2.7 - 7.3)
smokers	5 (IQR: 4.0 - 7.0)
non smokers	6 (IQR: 2.0 - 8.0)
Transcutaneous SpCO levels (%)	5 (IQR: 2 - 9)
smokers	6 (IQR: 3 - 7)
non smokers	5 (IQR: 2 - 10)

N=93 patients. Data are shown as No. and (%), mean (SD) or median with interquartile range (IQR: Q25-Q75) as appropriate

Y: year, CO: Carbon monoxide, COHb: blood carboxyhemoglobin, SpCO: blood carboxyhemoglobin determined by pulse CO-oximetry

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RESPIRATORY CARE Paper in Press. Published on March 19, 2013 as DOI: 10.4187/respcare.02313

Table 2. Performance characteristics of the RAD-57 pulse CO-oximeter for detecting CO poisoning, using 6% and 9% SpCO thresholds for non-smokers and smokers respectively.

	Non smokers N=56	Smokers N=37	All patients N=93
	SpCO ≥ 6%	SpCO ≥ 9%	SpCO ≥ 9%
Sensitivity	81.0% (58.1 - 94.6)	100% (47.8 - 100)	73.1% (52.2- 88.4)
Specificity	74.3% (56.7 - 87.5)	96.9% (83.8 - 99.9)	89.6% (79.7 - 95.7)
PPV	65.4% (44.3 - 82.8)	83.3% (35.9 - 99.6)	73.1% (52.2 – 88.4)
NPV	86.7% (69.3 - 96.2)	100% (88.8 - 100.0)	89.6% (79.7 - 95.7)

Data are shown as rate and 95% CI. Blood COHb levels used as the reference standard for the diagnosis of CO poisoning are: COHb > 5% in non-smokers and COHb > 10% in smokers and entire patient cohort.

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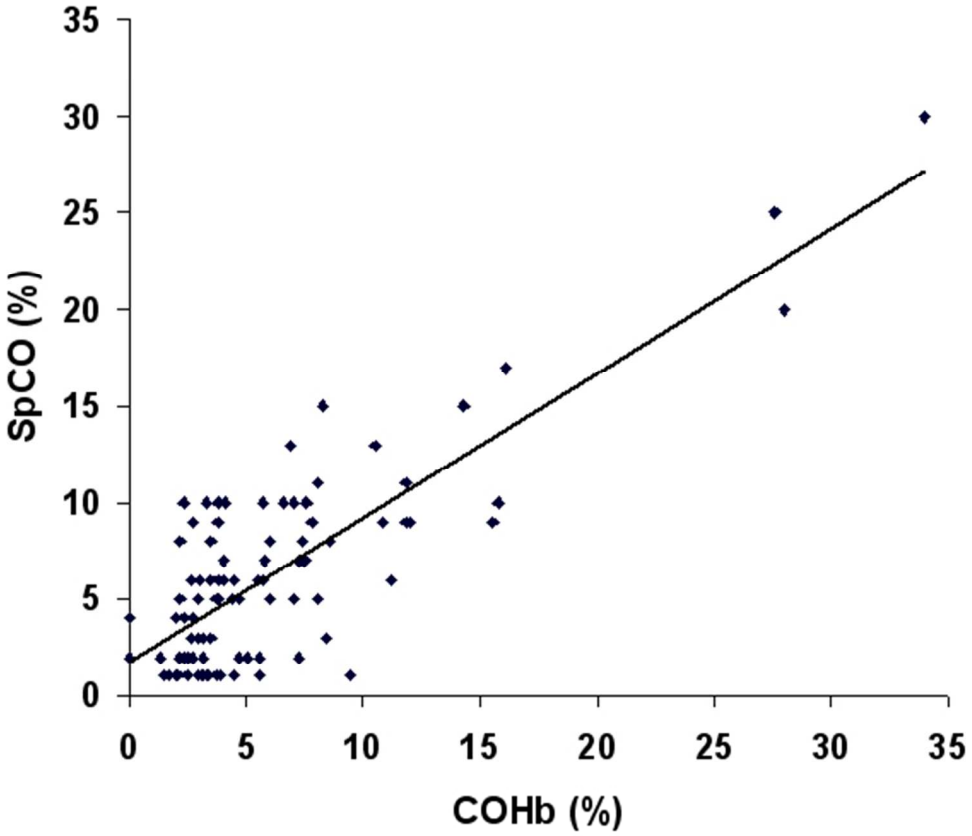

Figure 1
155x136mm (96 x 96 DPI)

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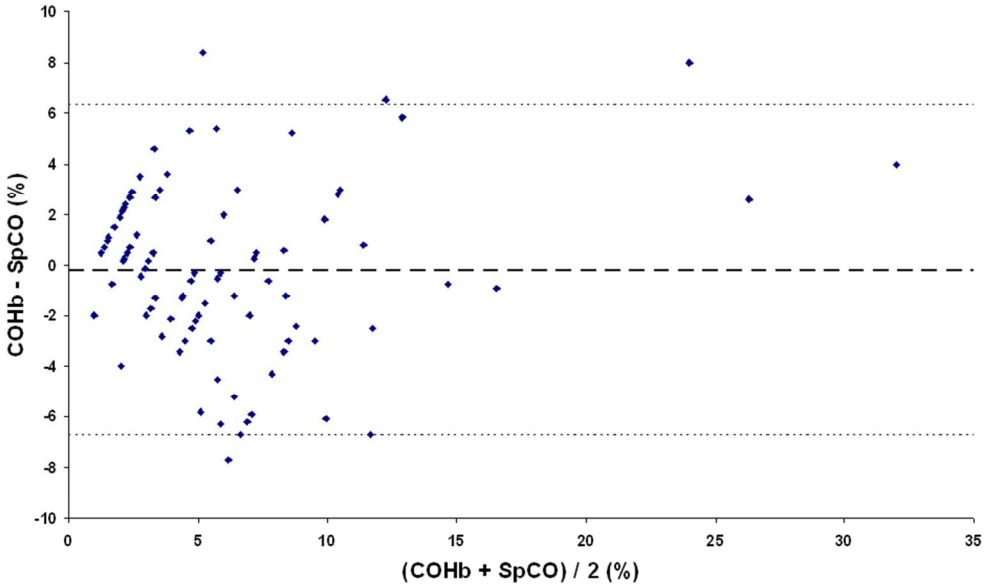

Figure 2A. All patients
252x152mm (96 x 96 DPI)

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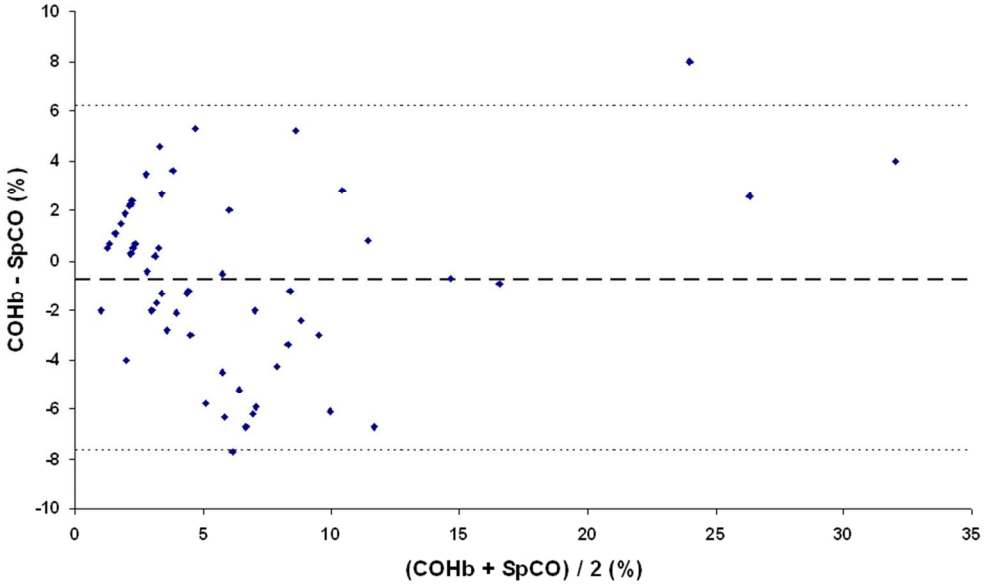

Figure 2B. Non smokers
253x153mm (96 x 96 DPI)

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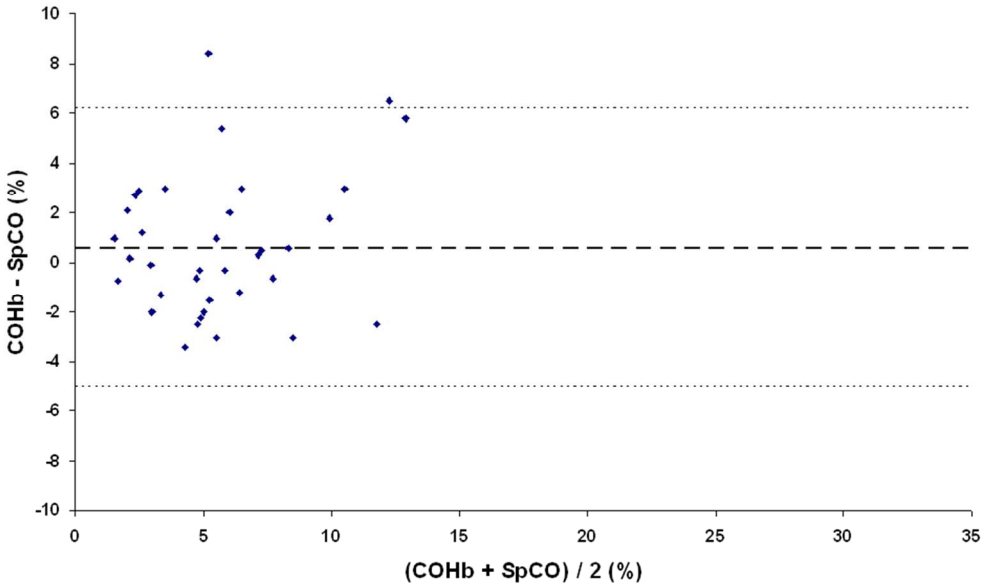

Figure 2C. Smokers
252x152mm (96 x 96 DPI)

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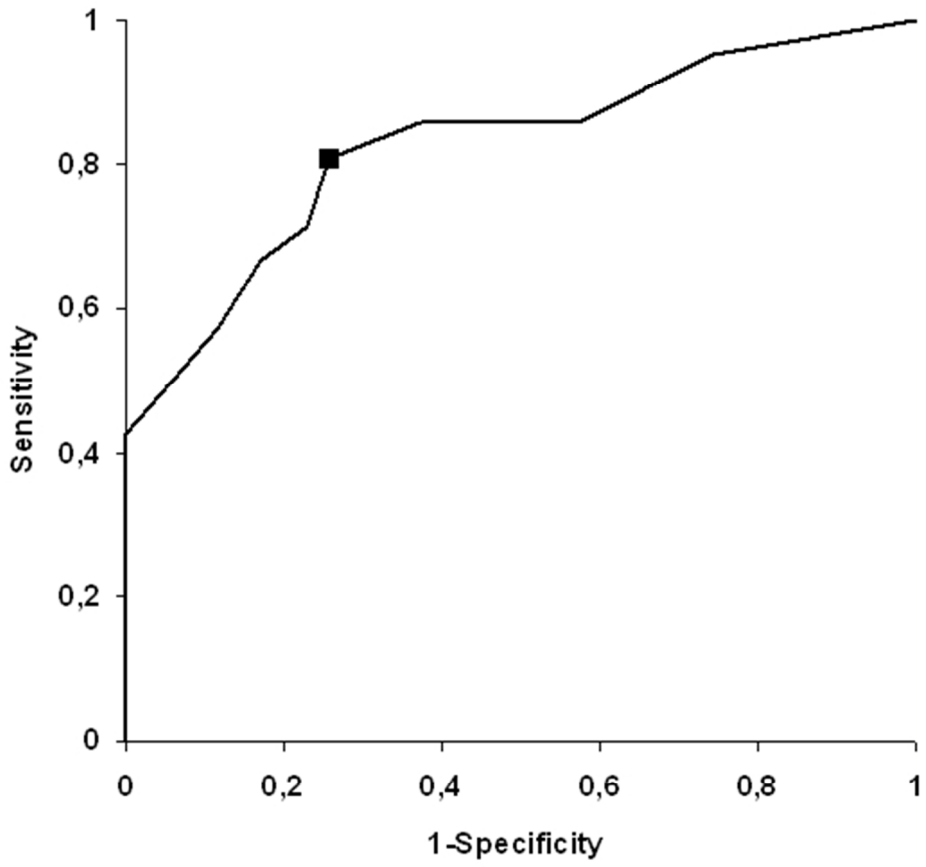

Figure 3A. Non smokers
147x132mm (96 x 96 DPI)

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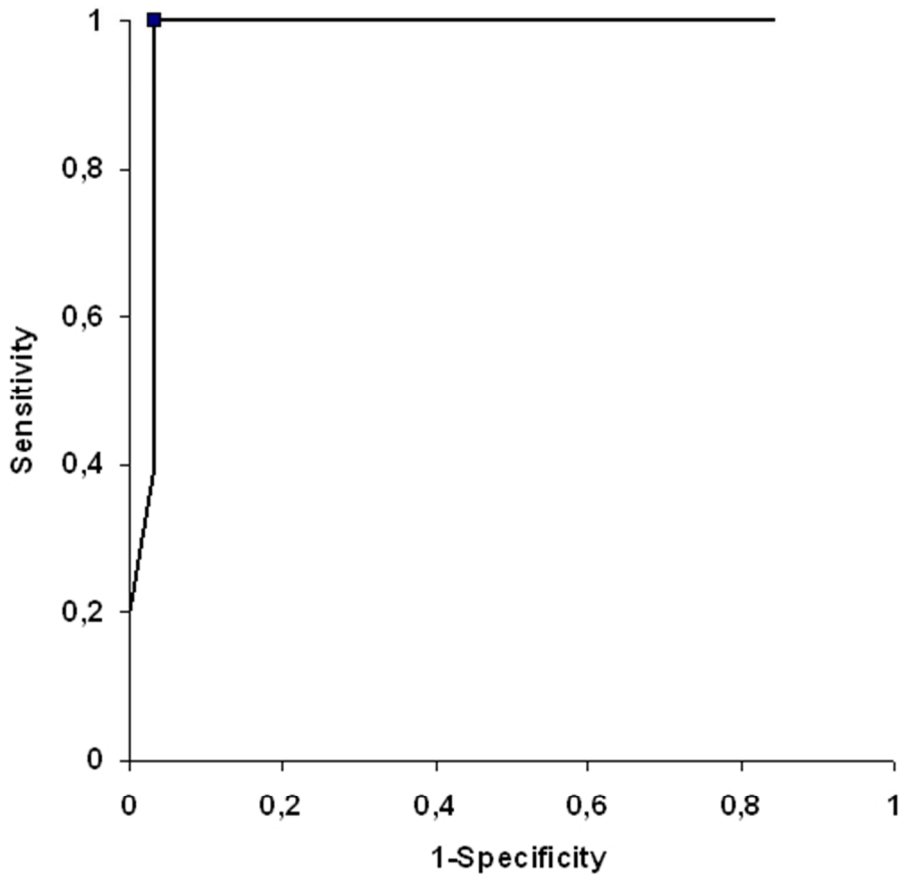

Figure 3B. Smokers
147x134mm (96 x 96 DPI)

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