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The measurement of exhaled carbon monoxide is influenced by airflow obstruction

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ABSTRACT: The concentration of carboxyhaemoglobin (COHb) is often estimated from measurements of carbon monoxide in the exhaled air (COexh). This study investigates whether the presence of airflow obstruction significantly alters the relationship between COexh and COHb.

Eighty-one regular smokers were prospectively studied and divided in four groups according to the presence and severity of airflow obstruction (none, mild, moderate, severe). In each subject, the authors measured in this order: 1) arterial blood gases; 2) haemoglobin concentration and COHb (by co-oxymetry); 3) COexh; 4) lung volumes; and 5) forced spirometry. The size of the measurement error (ΔCO) was calculated from the difference between COHb and COexh.

Neither the smoking history nor COexh were different in the four groups of subjects studied. In contrast, ΔCO increased in parallel to the degree of airflow obstruction. ΔCO was >2% (a threshold value normally used in the clinic to separate smokers from nonsmokers) only in patients with severe airflow obstruction. A stepwise multivariate analysis showed that both forced expiratory volume in one second (FEV1) (percentage reference) and COHb contributed significantly ($p<0.0001$) to predict ΔCO.

This study shows that the estimation of carboxyhaemoglobin from exhaled carbon monoxide measurements can be inaccurate in patients with severe airflow obstruction. In these patients, the direct measurement of carboxyhaemoglobin seems advisable in clinical practice.

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There is a direct relationship between the smoking status of a given individual and the concentration of carboxyhaemoglobin (COHb) in their blood [1, 2]. In practice, the latter is often assessed by measuring the concentration of carbon monoxide in the exhaled air (COexh), which is noninvasive, cheap, quick, portable, and does not require special technical background [3–8]. However, COexh will reflect COHb accurately only if the lung acts as an effective tonometer, and COexh is in dynamic equilibrium with COHb [1]. This may not be the case in patients with airflow obstruction, where the heterogeneity of expiratory time constants may significantly influence COexh readings [1, 3]. In fact, almost twenty years ago, JARVIS *et al.* [3] noted that COexh underestimated COHb in patients with radiological evidence of emphysema. In this investigation, however, the degree of functional impairment was not directly quantified. In the present study, the authors sought to define more accurately the potential effects of impaired lung function on the relationship between COexh and COHb and, in particular, to investigate whether the presence of airflow obstruction, which is common in smokers, alters (and to what extent) such a relationship. Given the widespread use of COexh measurements in clinical practice, a better delineation of factors potentially influencing it may have clinical value.

Material and methods

Study subjects

Eighty-one regular smokers (67 males, 14 females) who attended the authors′ pulmonary clinic for a variety of reasons were prospectively studied. They volunteered to participate in the study after being fully aware of its nature, characteristics, risks and potential benefits.

Study design

In each participant the authors measured, in this order: 1) arterial blood gases (oxygen tension in arterial blood (P_{a,O_2}), carbon dioxide tension in arterial blood (P_{a,CO_2}), pH); 2) haemoglobin concentration (Hb) and COHb; 3) COexh; 4) lung volumes; and 5) forced spirometry. The time between blood and expired gas sampling and the last cigarette was always >15 min.

To analyse the influence of airflow obstruction upon COexh measurements: 1) the size of the measurement error (ΔCO) was estimated by calculating the difference between COHb and COexh; 2) the forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratio was used to identify individuals without airflow obstruction (FEV_1/FVC: >81%) and patients with mild (FEV_1/

FVC: 61–80%), moderate (FEV1/FVC: 45–60%) and severe (FEV1/FVC: <45%) airflow limitation; 3) the values of ΔCO in these four groups were compared *via* analysis of covariance (ANOVA); and, 4) a stepwise multivariate regression analysis was used to analyse the influence of several functional variables of interest upon ΔCO.

Methods

Arterial blood samples were obtained anacrobically from the nondominant radial artery under local anaesthesia. P_{a,O_2}, P_{a,CO_2} and pH were immediately determined using an hourly-calibrated blood gas analyser (Instrumentation Laboratories; BG3, Instrumentation Laboratories, IZASA, Barcelona, Spain), and Hb ($g \cdot dL^{-1}$) and COHb (%) were measured using a weekly calibrated co-oxymeter (682; Instrumentation Laboratories). COexh was measured with a fuel cell type electrochemical sensor (EC50; Bedfont, Upchurch, Kent, UK), fitted with an internally mounted alcohol filter, and calibrated with a certified gas mixture with 50 parts per million (ppm) of CO (Carburos Metálicos, Barcelona, Spain). The patient was instructed to take a maximal inspiration from functional residual capacity (FRC). After a 20 s apnoea at total lung capacity (TLC), the patient was asked to exhale gently through a 20 cm long corrugated tube, ended with a nonreturn tee valve, fitted directly to the body of the analyser. As the sample capture is by diffusion (not by a pump), and as recommended by JARVIS *et al.* [4], to guarantee that an asymptotic reading had been reached, the highest COexh value recorded in the second of two successive readings was taken as indicative of the true CO alveolar concentration. To calculate ΔCO, COexh values (ppm) were expressed in percentage (as COHb) using the formula published by JARVIS *et al.* [4]. TLC, FRC and residual volume (RV) were measured in the sitting position by the helium dilution technique (Gold Standard; Collins, Braintree, MA, USA). Results are expressed as percentage of reference values [9]. FVC and FEV1 were measured (Gold Standard; Collins) in the sitting position; all manoeuvres were required to be reproducible within a ±5% range. Reference values were again from QUANJER *et al.* [9].

Analysis

Data is shown as mean±SD. Comparisons between groups were performed using a one-way analysis of variance (ANOVA), followed by *post hoc* contrast if appropriate. A stepwise multivariate regression method (p-value for entering the model (p_{in})=0.05; p-value for leavind the model (p_{out}) = 0.10) was used to analyse the influence of several independent variables upon ΔCO; the former were spirometric indices (FEV1, FVC, FEV1 /FVC, maximal mid-expiratory flow (MMEF)), air trapping parameters (RV, RV/TLC and TLC), blood gas data (P_{a,O_2}, P_{a,CO_2}) and COHb. *Post hoc* bivariate regression analysis was performed using the Pearson linear correlation test. A p-value <0.05 was considered significant.

Results

Table 1 presents the main results of the study. By design, the degree of airflow obstruction increased progressively in the four groups of subjects studied. Paralleling this increase, lung volume measurements and arterial blood gases deteriorated steadily (table 1).

Smoking history (pack-years) was not different between groups. COHb was slightly lower in the group of patients with mild airflow obstruction, but differences were marginal in absolute terms (table 1). COexh (both, ppm and percentage) was not different between groups. However, ΔCO was significantly different between groups (table 1).

Table 1. – The main anthropometric and functional variables of all the subjects studied, grouped according to the degree of airflow obstruction

	None	Mild	Moderate	Severe	p-value
n	19	18	26	18	
Age yrs	47±10	55±12	57±8	60±8	0.000
Pack-years	21±9	19±12	21±16	15±12	NS
FVC % ref	95±16	85±24	73±20	58±11	0.000
FEV1 % ref	97±17	74±22	46±13	26±7	0.000
FEV1/FVC %	84±3	71±6	51±4	36±6	0.000
MMEF % ref	93±21	46±18	16±5	9±3	0.000
FRC % ref	103±26	124±28	140±22	157±24	0.000
TLC % ref	98±13	106±20	111±16	111±12	NS
RV % ref	114±17	147±27	185±39	204±37	0.000
RV/TLC % ref	115±20	134±23	167±22	165±50	0.000
P_{a,O_2} mmHg	83±12	80±13	73±13	60±11	0.000
P_{a,CO_2} mmHg	35±3	36±8	40±5	46±6	0.000
Hb $g \cdot dL^{-1}$	14±3	15±2	16±2	16±3	0.03
COHb %	6.3±2.0	4.5±1.6	6.3±1.9	7.2±2.8	0.002
COexh ppm	26±12	17±9	22±9	21±11	NS
COexh %	4.8±1.9	3.4±1.5	4.1±1.5	4.0±1.8	NS
ΔCO	1.5±1.2	1.1±1.1	2.2±1.3	3.2±1.8	0.000

Data are presented as mean±SD. The p-values are derived from the analysis of variance (ANOVA) tests. FVC: forced vital capacity; % ref: percentage of reference value from QUANJER *et al.* [9]; FEV1: forced expiratory volume in one second; MMEF: maximal mid-expiratory flow; FRC: functional residual capacity; TLC: total lung capacity; RV: residual volume; P_{a,O_2}: oxygen tension in arterial blood; P_{a,CO_2}: carbon dioxide tension in arterial blood; Hb: haemoglobin; COHb: carboxyhaemoglobin; COexh: carbon monoxide in exhaled air; ppm: parts per million; ΔCO: measurement error.

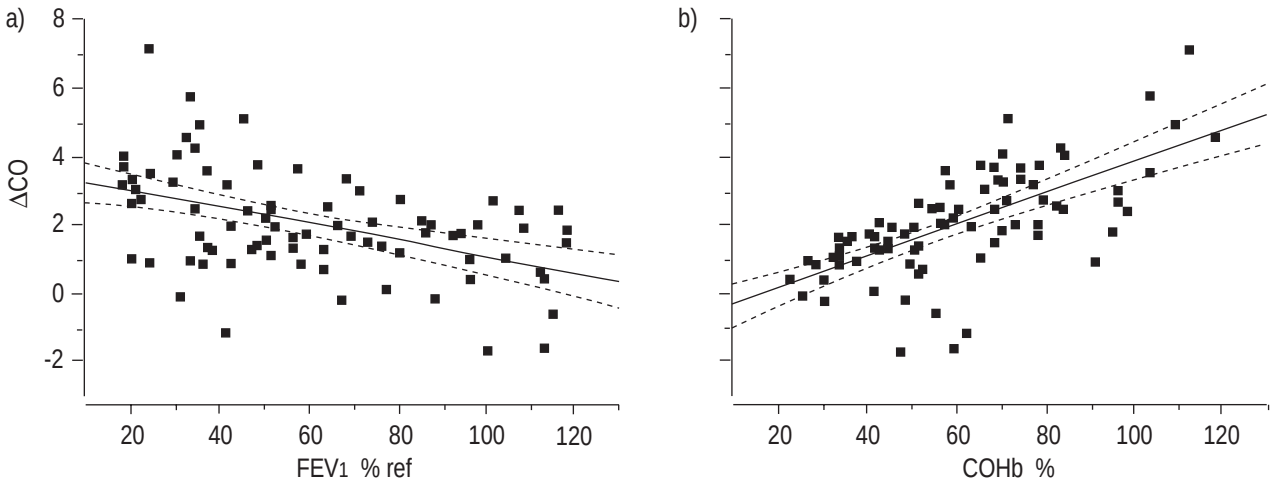

Fig. 1. – Relationship between the size of the measurement error (ΔCO) and a) forced expiratory volume in one second (FEV1) (r=-0.47, p<0.0001) and b) carboxyhaemoglobin (COHb) (r=0.66, p<0.0001). The solid lines correspond to the Pearson regression line, the dashed lines indicate the 95% confidence intervals and ■ are individual data points.

Of all the independent variables included in the multivariate analysis, only FEV1 and COHb entered the model and contributed significantly (p<0.0001) to predict ΔCO. Figure 1 shows the bivariate relationship between these two independent variables (FEV1 and COHb) and ΔCO.

Discussion

This study extends previous observations and confirms that the presence of airflow obstruction may significantly alter the estimation of COHb concentration from COexh measurements. This effect is particularly evident in patients with moderate to severe airflow limitation and in those with elevated COHb concentrations.

The measurement of COexh is widely used to estimate COHb and, as such, to monitor the smoking habits of patients [4–8]. This is an easy to use, portable, nonexpensive and noninvasive method and, in principle, it should provide an accurate estimation of COHb. However, JARVIS *et al.* [3] noted that the presence of radiological emphysema may interfere with its accuracy. The current investigation extends this former observation by quantifying the degree of airflow limitation present in the study subjects. As shown in figure 1 (a), the results show that the magnitude of the measurement error (ΔCO) increases in direct proportion to the degree of airflow obstruction (p<0.0001). This is not surprising because it is well established that the abnormal distribution of ventilation-perfusion ($\dot{V}'/\dot{Q}'$) ratios that occurs in patients with airflow obstruction [10–11] jeopardises the ability of the end-expiratory gas to reflect the average alveolar gas composition [12–14]. Yet, only in patients with severe airflow limitation, ΔCO was consistently >2% (table 1, fig. 1). Considering that a COHb concentration ≥2% is generally used in the clinical arena to separate smokers from nonsmokers [15], the current results indicate that the magnitude of ΔCO caused by airflow limitation is clinically relevant only in subjects with severe degrees of airflow obstruction. Nonetheless, it is precisely in these patients where an accurate evaluation of their smoking habits may have important clinical implications. For instance, these patients are often candidates for domiciliary oxygen therapy (DOT) [16–18] and, in these circumstances, active smoking is a clear environmental risk factor and a contraindication for DOT. Given that the results suggest that in patients with severe airflow limitation COexh measurements may be underestimating the real COHb value, and that the prescription of DOT inevitably requires the measurement of arterial blood gases, in these patients the authors would recommend the simultaneous determination of arterial blood gases and COHb in the arterial blood directly.

Figure 1 (b) also shows that the size of ΔCO was directly related to the concentration of COHb, indicating that the likelihood of a significant error increases in those individuals with high COHb concentrations. The relevance of this observation in clinical practice is probably small, because under these circumstances the important issue is to know whether or not the subject currently smokes, not its precise quantification [4–8]. Accordingly, an error in the estimation of COHb, when this is very high, is unlikely to influence any clinical decision. However, this effect may have important implications in epidemiological studies, aimed at quantifying as precisely as possible the degree of active smoking [10]. Figure 1 also shows that a few ΔCO values were negative. However, in absolute terms, differences were marginal in most of them. It is likely, therefore, that they are due to ΔCO. In any case, they do not influence the trend of the relationships shown in figure 1.

In summary, this study extends previous investigations and shows that carbon monoxide in exhaled air may underestimate carboxyhaemoglobin significantly in patients with severe airflow obstruction and in those with very high carboxyhaemoglobin concentrations. In practice, these observations should probably be taken into account when considering the possibility of indicating or continuing domiciliary oxygen therapy in patients likely to have severe airflow obstruction. In these cases, the direct measurement of carboxyhaemoglobin in blood is recommended.

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