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VALIDATION OF THE RESPIRATORY TOXICS EXPOSURE SCORE (RTES) FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE SCREENING

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Abstract
Objective: Our aim is to evaluate the validity of exhaled carbon monoxide (CO) and of a newly-created score as markers of Chronic Obstructive Pulmonary Disease (COPD). **Materials and Methods:** The CO level was measured in a derivation subsample of a cross-sectional study and linked to COPD diagnosis; its predictors were evaluated, and a scale was constructed. It was evaluated in a validation subsample and in a clinical setting. **Results:** Individuals with COPD had higher CO levels than healthy individuals. CO level significant predictors were cigarettes per day, waterpipes per week, lower age, male gender, living close to diesel exhaust, heating home with the use of diesel, and having indoor family smokers. A score composed of CO predictors was able to significantly predict COPD (Ora = 4–7.5). **Conclusions:** Coupled with the clinical judgment of physicians, this scale would be an excellent low-cost tool for screening COPD, in absence of spirometry.

Key words:
Carbon monoxide, COPD, Biomarker

BACKGROUND

Carbon monoxide (CO) is considered to be a major factor contaminating the Earth's atmosphere, whether outdoor or indoor [1]. It has well-known toxic effects on human beings, but its long-term chronic effects are still not very well-explored. Harmful cardiovascular and neuropsychological effects were most frequently associated with chronic exposure to low levels of carbon monoxide and carboxyhemoglobin [2]. In people with pre-existing diseases, CO pollution alone may result in increased morbidity and mortality [3]. Moreover, although colorless and non-irritating [4], CO has some oxidative damaging effect on respiratory cells, probably involved in the initiation or promotion of the damage produced in chronic respiratory diseases [5]: it has been linked to respiratory symptoms and decreased respiratory volumes in women of Guatemala exposed to biomass exhaust [6]; CO level in air has also been associated with emergency visits in people with Chronic Obstructive Pulmonary Diseases (COPD) [7].

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The main sources producing this contamination are engines using gasoline or diesel fuel during road transport and industrial processes using carbon compounds; these two are responsible for 80% of carbon monoxide emitted to the atmosphere [2]. CO is also a well-known indoor pollutant: it can originate as a result of the functioning of gas cookers and some heating systems, stationary combustion equipments, ingress of exhaust fumes from an attached garage, and proximity to heavily trafficked roads [8]. In a study performed in Guatemala, CO was used as a tracer for biomass combustion-related exposure [9]. Tobacco smoking is another important source of CO [10]; active cigarette and waterpipe smoking are both associated with CO increased exposure [11]. Moreover, CO is one of the most toxic substances present in the gas-phase of second-hand tobacco smoke [12]. It is noteworthy that combustion of any carbon-containing substance does not only produce CO; it could also produce other toxic gases, such as nitrogen oxides, sulfur oxides, aldehydes and polycyclic aromatic hydrocarbons, in addition to particulate matter, the deleterious effect of which can be added to those of CO [13].

Nevertheless, CO can be considered as an easy and rapid biomarker, i.e. primarily of interest for the assessment of the exposure and early biological effects in epidemiology as well as occupational and environmental medicine [10]: in fact, microenvironment measurements of CO were shown to represent well the personal exposures of individuals within that microenvironment; CO can be measured accurately by instrumental means and it therefore represents an ideal tracer of exposure [8]. Since biomarkers are "observable endpoints in the continuum of events ranging from exposure to diseases" [14], CO is considered to be both an exposure and effect biomarker [15]. Its concentration in exhaled air can be affected by multiple factors, including external exposure extent, its own toxic effects on cells and tissues [15], in addition to the presence of endogenous diseases, such as asthma and COPD [15,16]. CO is now considered as a marker useful to detect some environmental and occupational risk factors, particularly those typical of cities [17]; CO is also used as a screener for smoking during smoking cessation procedure [18], and a biomarker of oxidative stress implicated in the pathogenesis of many pulmonary diseases including chronic inflammatory lung disorders such as asthma and COPD [19–21]. Moreover, smokers with COPD have higher levels of exhaled CO versus healthy smokers [22].

COPD, although a disease of major importance in public health, is diagnosed only after spirometric evaluation according to GOLD guidelines [23]. The use of exhaled biomarkers as a diagnostic tool for COPD was overviewed by van Beurden and his collaborators in 2002, and he suggested that there was a need for "standardization of the measurements, for comparison of COPD patients with healthy persons matched for age and smoking-status, for data on reproducibility and variability, for correlation of exhaled markers with other parameters and for intervention studies" [24]. To our knowledge, no studies were specifically conducted to fulfill this need for exhaled CO. Moreover, in non-clinical settings where neither CO measurement nor spirometry is available, it is conceptually sound to search for a surrogate measure for the CO level that would hypothetically serve to predict COPD. The aim of the current analysis is to confirm the validity of carbon monoxide level in exhaled air as a biomarker of COPD in the general population, and to explore the validity of a score reporting exposure to pulmonary toxics as a marker for screening COPD in both epidemiological and clinical settings.

MATERIALS AND METHODS

Design and setting

Study 1: A cross-sectional study was carried out between October 2009 and September 2010, using a multistage cluster sample all over Lebanon. Lebanese residents aged 40 years and above were enrolled in the study, with no exclusion criteria. Additional details are presented in another publication [25].

Study 2: A case-control study was performed between July 2009 and June 2010, comparing a group of patients with COPD from two tertiary care hospitals in Beirut with a control group. Additional details of the study are also presented in another publication [26].

Procedures

In both studies, after an oral informed consent, subjects had a prebronchodilator spirometry in the presence of a trained technician and answered a standardized questionnaire. After the administration of two puffs of bronchodilator (Combivent®), a postbronchodilator spirometry was performed. The questionnaire comprised questions about sociodemographic characteristics, detailed active and passive smoking history, in addition to environmental and occupational toxic exposures questions. Moreover, carbon monoxide measurement was performed in a subsample of the first study population (derivation sample); the measurement was performed using a CO — Tester — NG, F.I.M. Every individual had to perform the measurement three times, and the best result was recorded.

Statistical analysis

For both studies, data entry was completed by independent lay persons that were unaware of the objectives of the study. Statistical analysis was performed using SPSS software, version 13.0. A p-value of 0.05 was considered significant. For continuous variables in the comparison of the groups, we used the Student's test for variables with adequate normal distribution. For non-normally distributed continuous variables and for non-continuous quantitative and ordinal variables, the Mann-Whitney test was used. For categorical variables, the Chi-square and Fisher's exact tests were used, when applicable. A linear trend test was applied to test for dose-effect relationships.

Dependent variables were: disease-related variables such as being diagnosed with COPD or not, chronic bronchitis, and respiratory symptoms. Independent variables were cigarette and waterpipe current and previous smoking, "toxics and fumes" occupational exposure, exposure to selected outdoor (living next to a busy road and living next to a local power plant — a diesel exhaust source) and indoor (heating home by gas, wood, or diesel, hot-air conditioner and passive smoking) pollutants. The carbon monoxide level was subsequently used as a dependent and an independent variable.

Multivariate analyses were carried out to evaluate predictors of dependent variables, taking into account potential confounding variables that had a p-value < 0.20 in bivariate analysis (gender, residency, age, height, weight, body mass index, education, work status, marital status) and independent variables cited above. When the dependent variable was continuous, a stepwise linear regression was applied to find out its predictors, after ensuring applications conditions (residuals linearity, model adequacy to data, and co-linearity diagnostics). This regression of predictors served to generate a score of exposure to toxic substances in the derivation subsample.

The above-mentioned score was later dichotomized according to the median. A kappa agreement measure was then calculated to evaluate the concordance between the dichotomous CO level and the toxic exposure score. In addition, sensitivity, specificity, positive predictive value and negative predictive value of the dichotomous score with respect to the dichotomous CO level were calculated.

Afterwards, in the validation subsample of study 1, a logistic regression was chosen because the dependent variable was dichotomous (disease variable; Chronic Obstructive Pulmonary Disease (COPD) and Chronic Bronchitis (CB)), after ensuring model adequacy to data by the Hosmer-Lemeshow test: a stepwise descendent likelihood ratio logistic regression was applied, and the final model was retained, the score of toxic exposure being the major independent variable. Point estimates of the ORa, 95% confidence intervals and p-values were presented. Similar methods were used in study 2.

RESULTS

CO level description (Subsample 1 of study 1)

In the subsample of study 1 where the CO level was measured (n = 652), CO had a minimum of 2 parts per million (ppm) and a maximum of 93 ppm. The CO level was then divided into quartiles, giving the following distribution: (2–6 ppm) 29%, (7–10 ppm) 25.6%, (11–20 ppm) 20.7% and (20–95 ppm) 24.7%.

CO level as a biomarker of respiratory diseases and symptoms (Subsample 1 of study 1)

Mean CO levels differences in the presence or absence of the diseases and symptoms are presented in Figure 1. We note that the CO level did not significantly differ between a patient with asthma and other individuals, i.e. the subgroup encompassing healthy individuals and those with respiratory diseases other than asthma (16.76 vs. 15.23; p = 0.247). In healthy individuals, the mean CO level was 13.04 (SD = 11.62).

The CO level was found to be an independent predictor of respiratory diseases: every unit of the CO level increase was associated with increased risk of COPD (OR = 1.055; p < 0.001). Moreover, the CO level units were also associated with increased risk of CB (OR = 1.033; p < 0.001), chronic cough (OR = 1.030; p = 0.001) and chronic sputum production (OR = 1.021; p = 0.006).

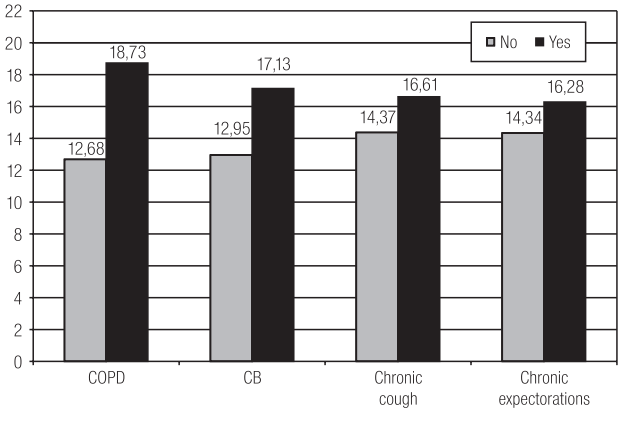

Fig. 1. Carbon monoxide level in chronic obstructive pulmonary disease (COPD), chronic bronchitis (CB), chronic cough and expectorations.

In Table 1, we present figures for dose-effect relationships between the CO levels and respiratory diseases and symptoms. Moreover, an inverse dose-effect relationship was also found between the CO level and the ratio of post-bronchodilator FEV1/FVC, reflecting a higher CO level in more severe obstruction: r = –0.149 (p < 0.001). Analogous results were found in the COPD patients subgroup, r = –0.115(p = 0.005); and what is more, in this subgroup, individuals treated with inhaled corticosteroids had a CO level that was lower than the non-treated ones (8.70 vs. 17.80; p < 0.001).

CO level predictors (Subsample 1 of study 1)

In Table 2, we present CO level predictors in the general population subsample where the CO level was measured (n = 652). The global correlation coefficient of the model with the CO level is 0.699, with an $R^2 = 0.489$, and an adjusted $R^2 = 0.483$. The ANOVA of the final model gave highly significant results (p < 0.001), with satisfactory residuals linearity and co-linearity diagnostics. We found that the CO level was predicted by age, cigarette and waterpipe current smoking, living next to a local power plant, exposure to passive smoking at home, and heating home by diesel (p < 0.05 for all; Table 2).

Respiratory toxics exposure score (RTES) creation (Subsample 1)

In the subsample 1 where the CO level was measured (n = 652), based on the previous regression, a score for respiratory toxics exposure was created. Its equation was the following:

$$\begin{aligned} RTES = {} & 19.20+(0.537\times cigarettes/\,day) \\ & +(2.359\times powerplant)-(0.121\times age)-(2.813\times gender)+ \\ & (2.138\times smokinside)+(2.319\times dieselheat) \\ & +(0.372\times waterpipe/week). \end{aligned} \quad [1]$$

Table 1. CO level and dose-effect relationship

CO level class	Prevalence of COPD	Prevalence of CB	Prevalence of cough	Prevalence of expectorations
2–6 ppm	3.4%	22.7%	10.6%	16.4%
7–10 ppm	12.6%	26.2%	19.8%	22.8%
11–20 ppm	16.9%	29.0%	24.4%	27.4%
21–95 ppm	18.1%	37.7%	20.5%	24.8%
p-value for trend	< 0.001	0.011	0.004	0.025

CO — carbon monoxide; COPD — chronic obstructive pulmonary disease; CB — chronic bronchitis.

Table 2. Carbon monoxide level predictors

Predictor	Beta	p-value	95% CI of beta
Cigarettes smoked per day (n)	0.537	< 0.001	0.482; 0.595
Waterpipes smoked per week (n)	0.372	0.009	0.012; 0.562
Age (years)	–0.121	< 0.001	–0.191; –0.069
Female gender	–2.813	< 0.001	–4.233; –1.394
Lives near a local power plant	2.359	0.002	0.873; 3.844
Family smokers smoke indoors	2.138	0.002	0.415; 2.872
Heating home with diesel fuel	2.319	0.002	0.864; 3.774

In this equation: [cigarettes/day: number of cigarettes/day; powerplant: living (1) or no (0) near a local power plant; age: age in years; gender: (1) if male and (2) if female; smokinside: home smokers smoke inside (1) or no (0); dieselheat: heating home by diesel (1) or not (0); waterpipe/week: number of waterpipes / week].

A correlation coefficient (r = 0.697) was found between the score and the CO level in parts per million.

RTES validation (Subsample 2 of study 1; study 2)

Afterwards, this score was used in the validation subsample 2 of study 1 (n = 1293), as an independent quantitative variable for predicting COPD: each unit increase in the RTES causes an increase of 1.13 in the ORa for COPD (Table 3); for CB, an identical ORa = 1.13 was found. Similar results were found for study 2 (clinical setting; n = 738: 211 COPD and 527 controls): ORa = 1.15 (1.11–1.18) (p < 0.001) for COPD and ORa = 1.14 (1.11–1.18) (p < 0.001) for CB, if the score is considered as a quantitative variable.

RTES binary classification and validation (Subsamples 1&2 of study 1; study 2)

RTES distribution in the subsample 1 of study 1 gave a median of 12.16. It was further classified as a binary exposure variable (RTES01) using 12 as the threshold value: individuals were considered exposed to respiratory toxics if they had a score equal to 12 or higher. Moreover, when dichotomizing the CO level around its median (= 10 ppm), we found an acceptable agreement coefficient between the RTES01 and the CO level (kappa = 0.538; p < 0.001). In this case, the sensitivity of RTES01 was found to be 77.54%,

Table 3. Toxic exposure score (RTES) association with chronic obstructive pulmonary disease (COPD)

Disease correlates	ORa	p-value	95% CI of ORa
Higher age class	2.31	< 0.001	1.98–2.70
Family history of respiratory disease	1.98	0.015	1.14–3.42
Previous waterpipe smoking	3.48	< 0.001	1.75–6.94
Previous cigarette smoking	4.37	< 0.001	2.66–7.19
Toxic exposure score (RTES)	1.13	< 0.001	1.10–1.16

ORa — odds ratio adjusted.

Table 4. Binary toxic exposure score (RTES01) association with chronic obstructive pulmonary disease (COPD)

Disease correlates	ORa	p-value	95% CI of ORa
Higher age class	2.18	< 0.001	1.86–2.56
Male gender	1.69	0.107	0.89–3.23
Family history of respiratory disease	2.00	0.010	1.19–3.39
Unemployed	2.22	0.032	1.08–4.55
Previous waterpipe smoking	2.77	0.003	1.41–5.43
Previous cigarette smoking	3.22	< 0.001	1.99–5.19
Binary toxic exposure score (RTES01)	4.91	< 0.001	2.98–8.08

ORa — Odds Ratio Adjusted.

while specificity was 76.24%, in addition to positive predictive value (77.84%) and negative predictive value (75.93%). This binary variable (RTES01) was further tested in subsample 2 of study 1 and presented in Table 4. In the general population, the RTES binary classification was strongly associated with COPD (ORa 4.91; $p < 0.001$). Moreover, RTES01 was also found to strongly correlate with chronic respiratory symptoms: CB (ORa = 4.41; $p < 0.001$), chronic cough (ORa = 3.19; $p < 0.001$) and expectorations (3.60; $p < 0.001$).

In study 2 (case-control; clinical setting), if the score was considered as a dichotomous variable (RTES01), we obtained a very strong association with respiratory diseases: ORa = 7.91 (4.54–13.78) ($p < 0.001$) for predicting COPD. Moreover, RTES01 was also found to strongly correlate with CB (ORa = 7.49; $p < 0.001$), chronic cough (ORa = 5.28; $p < 0.001$) and expectorations (5.52; $p < 0.001$).

DISCUSSION

In this study, as expected, we found that individuals with COPD and respiratory symptoms had CO levels that were higher than healthy individuals. These results were confirmed by a dose-effect relationship: with higher levels of CO in exhaled air, there was an incremental increase in the prevalence of COPD and respiratory symptoms. These results are similar to those reported by other researchers: in Guatemala, the CO level was correlated with chronic respiratory symptoms and volumes; but none of the women had COPD [6]. As a biomarker of effect, the biological plausibility of CO effect is known, since it can be a marker of oxidative damage, the latter being involved in COPD pathogenesis [5,19,20].

As for a biomarker of exposure, CO level significant predictors were the number of cigarettes smoked per day, the number of waterpipes smoked per week, lower age, male gender, in addition to living close to a local power plant

(a diesel exhaust source), heating home with diesel fuel, and having family smokers who smoke indoors. The factors we found were well-known sources of CO [2,8,10,12]; waterpipe smoking association with CO has also been previously reported by ourselves [11] and others [27]. Several of those factors are also known risk factors for COPD: cigarette smoking [28,29], waterpipe smoking [26], male gender [25], biomass fuel combustion [30], and passive smoking [31,32]. Thus, we were able to confirm the close relationship between the CO level, its predictors, and COPD. The elevation in the CO level can be due to exposure to incomplete combustion of carbon compounds, oxidative stress at the lung level, or both.

In the validation subsample of the epidemiological setting, we showed that a score composed of CO level predictors was able to predict COPD in a significant manner, whether considered as a quantitative variable or as a dichotomous variable. This was true and even stronger manifested in clinical settings. Although our strategy resembles that of Meijer et al., who developed a model for COPD prediction based on medical and work-related questions in an occupational setting [33], this is — to our knowledge — the first time a scale has been constructed based on the CO level prediction of COPD. Coupled with the diagnosis of the physician based on clinical symptoms, we expect this scale to be an excellent tool in screening for COPD, in the absence of spirometry. This could be considered a low-cost strategy to detect individuals marked with high risk of COPD.

Additional studies that take into consideration the clinical presentation of the patient would be necessary to further validate COPD prediction; the value of this new scale should also be tested in prospective studies. The limitations of our study include a possibility of selection bias in the cross-sectional study, and of information bias coupled with the questionnaire we used. However, the fact that our results were confirmed in both the epidemiological and clinical settings would lead us to override these risks. Furthermore, the lack of significant association of the CO level with asthma, the demonstrated dose-effect relationships and the multivariate analyses are considered strong points of this work.

CONCLUSION

In conclusion, we were able to create and validate a scale that would be used in clinical and epidemiological testing, as a tool to screen for COPD. Further studies, particularly taking into account the clinical symptoms of the individual, are necessary to evaluate its validity as a marker for COPD diagnosis.

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