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Journal of Addictive Diseases
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/wjad20

Does Breath Carbon Monoxide Measure Nicotine Dependence?

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Available online: 05 Oct 2010

To cite this article: Nestor D. Kapusta MD, Jakob Pietschnig MA, Paul L. Plener MD, Victor Blüml MD, MA, Otto M. Lesch MD & Henriette Walter MD (2010): Does Breath Carbon Monoxide Measure Nicotine Dependence?, Journal of Addictive Diseases, 29:4, 493-499

To link to this article: http://dx.doi.org/10.1080/10550887.2010.509280

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Journal of Addictive Diseases, 29:493–499, 2010
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ISSN: 1055-0887 print / 1545-0848 online
DOI: 10.1080/10550887.2010.509280

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Taylor & Francis Group

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ABSTRACT. The aim of the current study was the examination of exhaled breath carbon monoxide levels as a predictor for heaviness of smoking. In this regard, nicotine dependence was assessed among a representative sample of 1,870 Austrian male military conscripts in a cross-sectional setting. Participants completed the Heaviness of Smoking Index (a brief questionnaire for assessment of nicotine dependence), and their expired breath carbon monoxide levels were measured. The performance of carbon monoxide as a predictor of dependence levels was examined by means of Receiver-Operating-Characteristic Curve Analysis. Area Under the Curve, as well as sensitivity and specificity, were reported for each carbon monoxide cut-off level. The authors demonstrate that exhaled carbon monoxide levels serve as a satisfactory means to discriminate between smokers and non-smokers, yielding optimal discrimination at a cut-off level ≥ 5.5 parts per million (ppm), with a sensitivity of 95% and a specificity of 83%. However, the results indicate that carbon monoxide levels do not discriminate adequately between different levels of severity of nicotine dependence. The study demonstrates exhaled carbon monoxide as a useful marker of smoking status but not of nicotine dependence.

KEYWORDS. Heaviness of Smoking Index, HSI, smoking, nicotine dependence, carbon monoxide, sensitivity, specificity

INTRODUCTION

The assessment of smoking behavior and nicotine dependence has been under intense investigation in the past years. Clinicians and researchers search for noninvasive, reliable, and time- and cost-effective instruments for the classification of the severity of nicotine dependence to examine predictors of smoking behavior and its consequences for health and for monitoring smoking cessation efforts.

The progress of chemical analysis has allowed us to understand that carboxyhemoglobin[1] and carbon monoxide[2,3] are increased in blood and exhaled air of smokers when compared to non-smokers because, with more simple methods, carbon monoxide measurement in exhaled air has become the gold standard for "objective"

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detection of smoking status.[4,5] Criticism has been raised that such physiological measures may not be appropriate in the detection of low-level smokers. To overcome this gap, questionnaire-based self-reports on tobacco smoking have been suggested.[6–8]

The Heaviness of Smoking Index (HSI), a short two-item questionnaire of nicotine dependence,[9] has been originally derived from the Fagerström Tolerance Questionnaire.[10] This questionnaire is a very short measure of nicotine dependence comprising two items as detailed below. Validation studies show favorable scale properties of the HSI. It performed well in the assessment of adult smokers[11] and drug and alcohol dependent smokers,[12] and in comparison to other instruments among the male primary healthcare population,[13] smoking cessation patients,[14–16] and psychosocial units.[17] However, the validity of the HSI has been questioned among relatively light smokers[18] and has been recommended for the screening of high nicotine dependence.[19,20]

HSI items are associated with heritable temperament traits,[21] have good predicting properties of craving,[22] and represent the most highly heritable symptoms of nicotine dependence for both women and men.[23] The item "time to first cigarette in the morning" is a good single-measure for nicotine dependence.[9,24,25] Therefore, the HSI has been recommended for genetic research[23,24] and has become one of the standard measures in several recent genetic studies of nicotine dependence.[26–43]

The aim of the current study was to examine the relationship between different levels of nicotine dependence according to the HSI and breath carbon monoxide levels and to detect the sensitivity and specificity of the corresponding carbon monoxide cut-off levels.

METHODS

Military service or alternative service is mandatory for Austrian males, so every year all men who turn 18 are drafted for medical assessment to determine eligibility for National Service. Out of the military draft cohort in 2002, all 1,902 draftees of a military recruitment station in lower Austria were examined (representing a portion of 3.8% of the total 18-year-old Austrian male population in 2002). In the course of this assessment, draftees were asked to complete a paper-and-pencil questionnaire. Participants were assured full anonymity and that responses would have no impact on their National Service assessment. Smoking was not permitted during the examination process from 8.00 a.m. until the end of tests at 1.00 p.m. Full consent of the internal review board of the Medical University of Vienna was obtained preceding data collection.

Besides other questionnaires previously described,[44] the Heaviness of Smoking Index (HSI) was assessed. The HSI was validated by plasma and saliva cotinine, as well as carbon monoxide levels.[9,45] Both questions "How many cigarettes do you smoke per day?" (possible answers were "non-smoker," "10 or less," "11–20," "21–30," and "31 or more") and "When do you smoke your first cigarette in the morning?" (possible answers were "within 5 minutes," "6–30 minutes," "31–60 minutes," and "after more than 60 minutes") were scored between 0 and 3. In accordance with recent findings, a total HSI score of 4 or more is referred to as high nicotine dependence.[19,20] An HSI score of 0 to 3 is referred to as low nicotine dependence.

The HSI was administered following standard procedures of psychological assessment in the course of the military health assessment by trained instructors. In addition to the assessment of self-reports of smoking, a Smokerlyzer (EC50 Smokerlyzer; Bedfont Instruments; Kent, UK) was used to measure the level of carbon monoxide in exhaled air. All participants gave their full informed verbal consent to the procedure. The Smokerlyzer was operated by trained physicians according to standard procedures of the general health assessment of the Austrian Armed Forces. Data collection occurred over 7 weeks (up to 60 participants per day), allowing separate assessment of each participant individually while ensuring that time of test administration was identical for all participants to avoid moderating effects of time of day.

Data analysis was conducted using SPSS version 17.0 software (SPSS Inc., Chicago, IL) and R (R 2.11.1, R Foundation for Statistical

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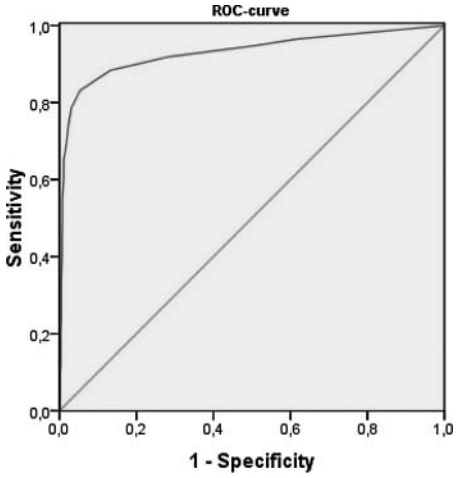
Computing, Vienna, Austria). To ensure satisfactory quality of data, two researchers performed data entry independently. Subsequently, data mismatches were identified and corrected. Of a total of 1,902 collected questionnaires, 32 questionnaires on tobacco were excluded from statistical analysis due to incomplete answers. Therefore, all subsequent analyses are based on a sample of 1,870 participants. Spearman correlation coefficients were calculated to assess associations between HSI items and carbon monoxide levels. To compare mean carbon monoxide values between groups, a t-test was applied. Analysis of variance (ANOVA) and post-hoc Scheffé tests were used to distinguish groups within item response categories. The performance of carbon monoxide as a predictor of dependence levels was examined with Receiver-Operating-Characteristic Curve Analysis (ROC). Area Under the Curve (AUC), as well as sensitivity and specificity, were reported for each carbon monoxide cut-off level. All omnibus tests were considered significant at the level of $P < .001$.

RESULTS

Non-Smokers versus Smokers

Of the 1,870 valid responses, 962 were smokers and had a mean score on HSI of 4.02 [standard deviation [SD] = 1.5]. Distribution of both carbon monoxide levels and scores of the HSI were skewed to the right. For ease of interpretation, parametric methods were used. Because evidence shows that non-normality of distributions do not exert substantial influences of results of parametric tests in large samples,[46,47] application of the t-test and ANOVA was justified. However, to substantiate these results, alternative non-parametric methods were applied. The mean maximum breath carbon monoxide level was 8.2 ppm (7.9) among the whole sample, 2.8 ppm (3.5) for non-smokers, and 13.2 ppm (7.5) for smokers ($P < .001$, Standard error of difference of means = 0.269; power > .99). Results of a Mann-Whitney U test were virtually identical ($P < .001$). Non-parametric ROC-analysis showed a nearly optimal AUC of .930 ($P < .001$, 95% confidence interval [CI] = .918, .942), with the best discriminating carbon monoxide value of ≥ 5.5 ppm between smokers and non-smokers with a sensitivity of 95% and a specificity of 83% (Figure 1). This indicates 5.5 ppm as the optimum cut-off level for discrimination between non-smokers and smokers.

FIGURE 1. ROC-curve for non-smokers and smokers. Note. Cut off level for classification of subjects' smoking status (smoker/non-smoker) at a carbon monoxide value of ≥ 5.5 ppm.



Categories of Nicotine Dependence

Categorization of the smokers according to the complete HSI-score (0 to 6) and application of these categories to the breath carbon monoxide led to a highly significant ANOVA model ($P < .001$; power > .99). Results of a Kruskal-Wallis test were virtually identical ($P < .001$). Scheffé-tests (considered significant at $P < .05$) suggested that smokers with a HSI-score of 0 can be looked on as a distinct group with the lowest carbon monoxide values compared to the other groups (9.6 ppm [6.2]; all $P < .01$ for all group comparisons). The HSI-score groups 1, 2, and 3 can not be distinguished statistically from each other, but on average show lower carbon monoxide values (13.7 ppm [7.4]; all P-values > .54 for group comparisons 1, 2, and 3) than the HSI-score groups 4, 5, 6, which again form a homogeneous subgroup (16.9 ppm [7.7]; all Pvalues > .88 for group comparisons 4, 5, and 6). These three groups will further be denoted as occasional, medium dependent, and highly

TABLE 1. Performance of Carbon Monoxide (CO) as a Screening Marker for Different Nicotine Dependence Levels

Non-Smokers (N = 908) vs.	AUC	Sensitivity (%)	Specifity (%)	CO (ppm)	*N*
Occasional smokers (HSI = 0)	.873	78	87	4.5	220
Low dependence (HSI = 0–3)	.923	87	87	4.5	817
Medium dependence (HSI = 1–3)	.942	85	95	5.5	597
High dependence (HSI ≥ 4)	.968	94	95	5.5	145

AUC = Area Under the Curve; CO = Carbon monoxide; ppm = parts per million; HSI = Heaviness of Smoking Index.

dependent smokers. An examination of the discrimination of non-smokers versus different levels of nicotine dependence yielded a sensitivity of 78% to 94% and a specificity of 87% to 95% at a carbon monoxide cut-off level of ≥ 4.5 or 5.5 ppm (Table 1).

Discrimination Between Levels of Nicotine Dependence

Regarding the discriminating power of breath carbon monoxide between occasional and medium dependent smokers, ROC analysis resulted in an AUC of .667 (95% CI = .626, .709), with an optimum discriminating carbon monoxide value of 12.5 ppm, a sensitivity of 54%, and a specificity of 75%. Using the breath carbon monoxide to discriminate between medium and highly dependent smokers resulted in an AUC of .626 (95% CI = .575, .677), with a carbon monoxide value of 15.5 ppm yielding a sensitivity of 57% and a specificity of 63%. The discrimination between low (12.6 ppm [7.3]) and high dependence showed a slightly higher AUC of .665 (95% CI = .609, .680) with breath carbon monoxide optimum discrimination at 15.5 ppm, with a sensitivity of 57% and a specificity of 68%.

DISCUSSION

Our study demonstrates that exhaled carbon monoxide is useful to predict smoking status in young adult males (being a non-smoker or a smoker) when using a cut-off level of 5.5 ppm. The sensitivity and specificity depends on the severity of nicotine dependence, with higher dependence resulting in higher accuracy (AUCs ascending in order of level of dependence) (Table 1). Although several earlier studies recommended a carbon monoxide cut-off level higher than 8 or 9 ppm,[3,5,6,8,48,49] more recent studies have recommended carbon monoxide cut-off levels of 6 ppm for outpatients, 5 ppm for military personnel, and 6 ppm for the general population, which are comparable to our results.[50–52] However, even lower values, as low as 2 to 3 ppm, were recently suggested to identify smokers.[53] Different cut-off recommendations may result from different populations examined because age, sex, and environmental factors were recognized to influence carbon monoxide levels in healthy non-smokers[54] and patients with pulmonary diseases such as asthma and Chronic Obstructive Pulmonary Disease (COPD) may need higher cut-off levels.[55] Our naturalistic sample of 1,870 18-year-old men represents the norm carbon monoxide value of this population. In contrast to other markers, such as nicotine,[56] cotinine,[48] or thiocyanate,[57] which demand plasma, saliva, or urine testing, carbon monoxide measurement is easily and inexpensively applicable in epidemiological and clinical settings.

The first relationship of carbon monoxide and smoking has been established during a period when a more differentiated concept of nicotine dependence was absent. Since then, carbon monoxide has been recommended as a marker of "smoking."[4,5] As shown in our study, carbon monoxide only poorly differentiates between different levels of nicotine dependence. Therefore, it seems that carbon monoxide is not useful for assessment of a more complex concept of nicotine dependence, including the dimensions of craving and withdrawal or even the elaborated multifaceted dimensions of the DSM-IV.[58] It should be noted that alternative forms

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of smoking that may influence exhaled breath carbon monoxide (e.g., tobacco pipe) were not assessed in the current study. Although this might be a reason for the poor discrimination of carbon monoxide levels regarding severity of smoking, it is unlikely that differentiation between smokers and non-smokers is affected given the typically high co-occurrence of different types of smoking.[44,59,60]

Thus, based on our results, we only can recommend carbon monoxide as a single screening measure or as an adjunct to self-reports on smoking status (smoker vs. non-smoker) but not as a marker of nicotine dependence. The carbon monoxide-derived smoking status is useful in situations where self-reports may be biased toward a socially desirable response,[61] e.g., among younger study participants, when administering self-rating questionnaires, or to confirm abstinence in smoking cessation settings.[8]

The contrast between the performance of carbon monoxide as a marker of smoking or non-smoking rather than nicotine dependence reflects the weakness of carbon monoxide to detect nicotine dependence, as previously described.[6–8] However, it could also reflect a low validity of HSI among light smokers, which also has been discussed prior to us.[18] Thus, the structure of HSI items suggests that besides the proposed binary HSI use to detect low and high nicotine dependence[20,62] an additional category of "occasional smokers" (HSI = 0) could be considered. This group of smokers, which also reflects experimental users, decreases the sensitivity and specificity of the breath test and should be taken into consideration when collecting self-reports on smoking.

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