EXHALED CARBON MONOXIDE LEVELS AMONG MALAYSIAN MALE SMOKERS WITH NICOTINE DEPENDENCE

Ng Chong Guan[1,2] and Anne Yee Hway Ann[1]

[1]Department of Psychological Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur; [2]University Malaya Centre for Addiction Sciences, Petaling Jaya, Selangor, Malaysia

Abstract. We studied the use of exhaled carbon monoxide (CO) to identify nicotine dependence among adult Malaysian male smokers. We conducted a cross-sectional study among 107 male smoking staff at a university hospital. We measured their exhaled CO using a piCO$^+$ Smokerlyzer and diagnosed nicotine dependence using a Mini-International Neuropsychiatric Interview (MINI). The optimal cut-off value for exhaled CO was determined. The correlation between exhaled CO level and the Fagerstrom Test for Nicotine Dependence (FTND) was also assessed. The mean exhaled CO level among subjects with nicotine dependence (15.78 ppm) was significantly higher than subjects without nicotine dependence (9.62 ppm). The cut-off value used to identify smokers with nicotine dependence was set at 10 ppm (specificity=0.721, sensitivity=0.731, positive predictive value=0.817 and negative predictive value=0.617). Psychometric properties were stable with various durations of smoking. Exhaled CO correlated positively with FTND scores (Pearson's rho=0.398, p=0.01). Our findings show exhaled CO can be used to identify nicotine dependence among adult Malaysian male smokers.

Keywords: exhaled carbon monoxide, smoker, nicotine dependence, male, validation

INTRODUCTION

Smoking is associated with various diseases including cancer. Despite this knowledge, about one third of the adult male global population smoke (Brundtland, 2000). The World Health Organization (WHO) reports smoking causes 4 million deaths globally every year (WHO, 2010). In Malaysia, about half of Malaysian men smoke. Every year, nearly 10,000 people in Malaysia die from smoking-related diseases (Information research lab, 2010).

There are several stages in tobacco use. It usually begins with experimental use typically because of peer pressure, and is done for recreation. This is followed by regular use and increasing tolerance. In the final stage, the person develops nicotine dependence. Nicotine dependence is characterized by tolerance and withdrawal symptoms (Sadock and Sadock, 2005) Based on DSM IV TR (Diagnostic

Correspondence: Ng Chong Guan, Department of Psychological Medicine, University Malaya Medical Centre, 59100 Kuala Lumpur, Malaysia.
Tel: 603 7949 2068; Fax: 603 7955 6477
E-mail: chong_guan1975@yahoo.co.uk

and Statistical Manual of Mental Disorders. 4th ed Text Rev) criteria, a smoker is diagnosed with nicotine dependence if they meet three of seven criteria: spending a great deal of time getting, using, or getting over the effects of cigarettes, smoking more often or in larger amounts than intended, tolerance, use prevents participation in activities, emotional or psychological problems, health problems and wanting or trying to quit or cut down (American Psychiatric Association, 2000).

It is important to identify smokers with nicotine dependence, to give appropriate advice regarding cessation. This is often assessed using self-rated questionnaires, which may predispose to inaccurate responses and contribute to under diagnosis (Coultas *et al*, 1988; American Psychiatric Association, 2000). The measurement of exhaled carbon monoxide (CO) provides an immediate and non-invasive method of assessing smoking status. CO displaces oxygen in erythrocytes to form carboxyhemoglobin (COHb). The half-life of COHb is about 5 to 6 hours and may remain in the blood for up to 24 hours depending on a number of factors, such as the level of physical activity and environmental CO exposure. With breath holding, CO in the blood forms an equilibrium with CO in alveolar air; therefore, there is a high degree of correlation between exhaled CO levels and COHb concentration (Peterson and Stewart, 1970; Joumard *et al*, 1981; Colletti *et al*, 1982; Crowley *et al*, 1989; Deller *et al*, 1992). The cut-off value of exhaled CO to distinguish a smoker from a non-smoker has been extensively studied and is estimated to be 6-8 ppm (parts per million) (Joumard *et al*, 1981; Crowley *et al*, 1989; Deller *et al*, 1992; Middleton and Morice, 2000). However, it is unclear what cut-off level of exhaled CO among smokers reflects nicotine dependence.

We measured exhaled CO to determine the cut-off level of nicotine dependence among adult Malaysian male smoker. We also compared exhaled CO levels with the scores of the Fagerstrom Test for Nicotine Dependence (FTND), a self-rated questionnaire assessing nicotine dependence (Fagerstrom and Schneider, 1989).

MATERIALS AND METHODS

Study design

We carried out a cross-sectional study to determine the exhaled CO levels among smokers with nicotine dependence. This study was approval by the Medical Ethics Committee (MEC), University Malaya Medical Centre, Kuala Lumpur. Permission to use the FTND was obtained from the original author. One hundred seven of male staff members of the University Malaya Medical Centre who smoked were included in the study after informed consent was obtained. They were reassured of confidentiality to encourage accurate reporting of smoking habits. Background information about their ages, years of smoking, smoking habits, educational levels and marital status were collected. The subjects were given information about the Smorkerlyzer which measured their exhaled CO. They were interviewed by the second author for nicotine dependence using the Mini-International Neuropsychiatric Interview (MINI). Then they were given the FTND to complete.

Exhaled CO measurement

Exhaled CO was measured using the piCO$^+$ Smokerlyser (Bedfont Scientific, Harrietsham, England), a portable CO monitor. The Smokerlyser measures exhaled CO in parts per million (ppm CO).

During breath holding, the CO in the blood forms an equilibrium with CO in the alveolar air; therefore, there is a high degree of correlation between exhaled CO level and COHb concentration. A standard procedure was used with the measurement. The subjects were asked to exhale completely, inhale fully, and then hold their breath for 15 seconds. Subjects were then asked to exhale slowly into the Smokerlyser. They were encouraged to exhale fully in order to sample the alveolar air. If the subject could not hold their breath for 15 seconds, they were asked to commence exhalation at a comfortable point, but to exhale completely. The time from the last cigarette smoked prior to the test was recorded.

Mini-International Neuropsychiatric Interview (MINI)

The diagnosis of nicotine dependence was made using the Mini-International Neuropsychiatric Interview (MINI). It is a short structured diagnostic interview, developed for psychiatric disorders listed in the DSM-IV and ICD-10. The administration of MINI takes approximately 15 minutes. It is designed to be a short, accurate structured psychiatric interview for clinical trials and epidemiology studies. The nicotine dependence module of the MINI includes seven questions answered in a Yes-No response format, which reflects the elements of the DSM-IV and ICD-10 definitions of nicotine/tobacco dependence: tolerance, withdrawal, nicotine is used in larger amounts or for longer periods than intended, persistent desire or unsuccessful efforts to cut down, a great deal of time is spent to acquire or use the nicotine, important activities are given up or reduced because of nicotine use, and nicotine use is continued even with the knowledge of its harmfulness. The subjects are considered dependent if they experienced three or more symptoms during the previous 12 months (Sheehan *et al*, 1998).

Fagerstrom Test for Nicotine Dependence (FTND)

The Fagerstrom Test for Nicotine Dependence (FTND) is a self-reported questionnaire which is easy to use and gives immediate feedback with good sensitivity and specificity to assess the nicotine dependence of smokers for clinical treatment and research (Heatherton *et al*, 1991). FTND contains 6 items derived from the eight-item Fagerstrom Tolerance Questionnaire (FTQ) (Fagerstrom and Schneider, 1989). The six items are: the time to the first cigarette after awakening, difficulty in refraining from smoking in forbidden places, the hardest cigarette of the day to give up, the number of cigarettes smoked per day, the ability to smoke less during the first hours after awakening compared to the rest of the day and the ability to stop smoking in case of sickness (Heatherton *et al*, 1991).

Statistical analysis

The results were analyzed with the SPSS statistical package (SPSS; Chicago, IL). Descriptive statistics were used to examine baseline characteristic data. The independent *t*-test was used to test for a significant difference between the exhaled CO levels of smokers with and without nicotine dependence. The adjusted mean difference was calculated using a multiple linear regression model including age, years smoked and last cigarette smoked as covariates. The cut-off level for exhaled CO among smokers with nicotine dependence was determined from co-ordinate points when the sensitivity and specificity were optimal using the Receiver Operating Characteristic (ROC) analysis using the MINI as the standard diagnostic test.

Positive and negative predictive values were calculated. The Area Under the Curve (AUC) for the ROC was determined. Sensitivity analysis was conducted for different durations of smoking. The pearson's correlation was used to examine the relationship between exhaled CO level and the FTND result.

RESULTS

Of 107 male staff members who participated in the study, the mean age was 36 years old. The average age subjects started smoking was 20 years old and the average length of smoking was 17 years. The majority of subjects were Malays, married with at least a secondary level education (Table 1).

Of 107 subjects, 67 had nicotine dependence. The average exhaled CO level among subjects with nicotine dependence (15.78) was significantly higher than those without dependence (9.62) (Table 2).

The area under the receiver operating characteristic curve (AUC) was 0.751 (95% CI 0.648-0.855). The optimal cut-off CO level to distinguish smokers with and without nicotine dependence was 10 ppm, with a sensitivity of 0.731, a specificity of 0.721, a positive predictive value of 0.817 and a negative predictive value of 0.617 (Table 3).

For subjects with different lengths of smoking history, the cut-off value of 10 ppm for exhaled CO had a good sensitivity (0.625-0.900) and positive predictive

Table 1
Baseline demographic characteristics of study subjects (*N*=107).

Variable	Mean	SD
Age	36.42	11.47
Age started to smoke	19.61	5.47
Years smoked	16.93	10.37
	N	%
Race		
Malay	100	93.5
Chinese	1	0.9
Indian	4	3.7
Other	2	1.9
Education		
Primary	6	5.6
Secondary	80	74.8
Tertiary	21	19.6
Marital status		
Married	73	68.2
Never married	34	31.8

Table 2
Comparison of carbon monoxide (CO) levels between smokers with and without nicotine dependence[a].

Smoker	*N*	CO level Mean (ppm)	Mean difference	Adjusted mean difference (B)	95% CI	*p*-value
With nicotine dependence	67	15.78	6.151	5.793[b]	2.533-9.052	0.001
Without nicotine dependence	40	9.62				

[a]Nicotine dependence was diagnosed using the MINI.
[b]Adjusted for age, years smoked and time of last cigarette smoked prior to the exhaled CO measurement.

value (0.769-1.000) for identifying nicotine dependence. The specificity (0.571-1.00) and negative predictive value (0.438-0.889) varied depending on the number of years smoked (Table 4).

The exhaled CO level was positively correlated with the FTND score (Table 5).

DISCUSSION

In this study, we examined exhaled CO levels among 107 Malaysian adult male smokers working at a university hospital. The mean exhaled CO level among subjects with nicotine dependence (15.78 ppm) was significantly higher than subjects without nicotine dependence (9.62 ppm). The cut-off value to distinguish smokers with and without nicotine dependence was 10 ppm, with a specificity of 0.721, a sensitivity of 0.731, a positive predictive value of 0.817 and a negative predictive value of 0.617. The psychometric properties were relatively stable across different durations of smoking. Exhaled CO was positively correlated with the FTND score.

There were several limitations in this study which should be highlighted. First, exhaled CO levels are influenced by physical activity levels, which were not measured in this study. Second, passive exposure to CO increases CO in the blood and consequently exhaled CO. We assumed passive exposure in the working place was relatively similar but not outside work. Third, physical illness can affect a subject's inhalation intensity and exhaled CO level. Information regarding physical illness and respiratory diseases

Table 3
Sensitivity and specificity for each coordinates for the receiver operating characteristic curve of exhaled CO level to determine nicotine dependence among smokers using the MINI.

CO level (ppm)	Sensitivity	Specificity
7.0	0.896	0.550
8.0	0.821	0.575
9.0	0.761	0.650
10.0	0.731	0.725
11.0	0.701	0.750
12.0	0.642	0.800
13.0	0.567	0.800

Table 4
Sensitivity of analysis using an exhaled CO cut-off level of 10 ppm to identify nicotine dependence based on the MINI for different lengths of time smoked.

Years smoked	Using an exhaled CO level > 10 ppm to identify subjects with nicotine dependence based on the MINI			
	Sensitivity	Specificity	PPV	NPV
< 10	0.625	0.778	0.882	0.438
10 to < 20	0.714	1.000	1.000	0.625
20 to < 30	0.833	0.571	0.769	0.667
≥ 30	0.900	0.571	0.600	0.889

CO, carbon monoxide; ppm, parts per million; PPV, positive predictive value; NPV, negative predictive value

Table 5
Correlation between exhaled CO levels and FTND scores.

	FTND score	*p*-value
CO level (ppm)	0.398	0.01

was not collected in this study (Joumard *et al*, 1981; Jarvis *et al*, 1984; Deller *et al*, 1992).

There have been many studies looking at the association between exhaled CO level and smoking status. The cut-off value for a smoker has been estimated to be 6-8 ppm (Crowley *et al*, 1989; Middleton and Morice, 2000). It varies depending on several factors, such as gender, number of cigarettes smoked, physical activity and ethnicity. Smoking eventually leads to dependence. Instead of using a self-rated questionnaire to determine nicotine dependence among smokers, which is prone to inaccurate responses a biomarker, such as exhaled CO, can provide an easy-to-use, noninvasive option. There is limited information about the cutoff value of exhaled CO to identify smokers with nicotine dependence. In this study, we demonstrated that an exhaled CO level can distinguish smokers with and without nicotine dependence with good psychometric performance.

There is controversy regarding the use of exhaled CO to determine smoking status, since it reflects only short term exposure to tobacco smoke. Combining its use with other biomarkers with longer half lives, such as serum cotinine and salivary thiocyanate (in the plasma, saliva or urine) have seen suggested (Waage *et al*, 1992; Morabia *et al*, 2001). In this study, we demonstrated using a cut-off level for exhaled CO of > 10 ppm could identify smokers with nicotine dependence. The result was highly sensitive even among subjects with different lengths of smoking.

In conclusion, an exhaled CO level of 10 ppm may be used to identify nicotine dependence among adult Malaysian male smokers.

ACKNOWLEDGEMENTS

We would like to thank the staff from University Malaya Medical Centre who participated in this study.

REFERENCES

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington DC: American Psychiatric Association, 2000.

Brundtland GH. Achieving worldwide tobacco control. *JAMA* 2000; 284: 750-1.

Colletti G, Supnick JA, Abueg FR. Assessment of the relationship between self-reported smoking rate and Ecolyzer measurement. *Addict Behav* 1982; 7: 183-8.

Coultas DB, Howard CA, Peake GT, *et al*. Discrepancies between self-reported and validated cigarette smoking in a community survey of New Mexico Hispanics. *Am Rev Respir Dis* 1988; 137: 810-14.

Crowley TJ, Andrews AE, Cheney J, *et al*. Carbon monoxide assessment of smoking in chronic obstructive pulmonary disease. *Addict Behav* 1989; 14: 493-502.

Deller A, Stenz R, Forstner K, *et al*. The elimination of carboxyhaemoglobin: gender specific and circadian effects. *Infusther Transfusmed* 1992; 19: 121-6

Fagerstrom KO, Schneider NG. Measuring nicotine dependence: a review of the Fagerstrom Tolerance Questionnaire. *J Behav Med* 1989;12: 159-82.

Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom test for

nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Brit J Addict* 1991; 86: 1119-27.

Information research lab. Smoking death data, 2010. [On line]. [Cited 2010 Jun 29]. Availabe from: URL: http://www.inforeseachlab.com/smokingdeaths.chtml

Jarvis MJ, Tunstall-Pedoe H, Feyerabend C, *et al*. Biochemical markers of smoke absorption and self-reported exposure to passive smoking. *J Epidemiol Community Health* 1984; 38: 335-9.

Joumard R, Chiron M, Vidon R, *et al*. Mathematical models of the uptake of carbon monoxide on hemoglobin at low carbon monoxide levels. *Environ Health Perspect* 1981; 41: 277-89.

Middleton ET, Morice AH. Breath carbon monoxide as indicator of smoking habit. *Chest* 2000; 117: 758-63.

Morabia A, Bernstein MS, Curtin F, Berode M. Validation of self-reported smoking status by simultaneous measurement of carbon monoxide and salivary thiocyanate. *Prev Med* 2001; 32: 82-8.

Peterson JE, Stewart RD. Absorption and elimination of carbon monoxide by inactive young men. *Arch Environ Health* 1970; 21: 165-71.

Sadock B, Sadock A. Nicotine-related disorders. Kapplan and Sadock's comprehensive textbook of psychiatry. 8th ed. Philadelphia: Lippincott Williams & Wilkins, 2005: 1257-64.

Sheehan DV, Lecrubier Y, Sheehan KH, *et al*. The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998; 59: 22-33.

Waage H, Silsand T, Urdal P, Langard S. Discrimination of smoking status by thiocyanate and cotinine in serum, and CO in expired air. *Int J Epidemiol* 1992; 21: 488-93.

World Health Organization (WHO). World health statistics 2010. Geneva: WHO, 2010. [Cited 2010 Jun 29]. Available from: URL: http://www.who.int/whosis/whostat/20102010/en/index.html