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Research Paper

Do nicotine intake and acute heart rate response to smoking rank nicotine dependence the same?

Jerome F Walker[1,*], Paul D Loprinzi[2], Christy J Kane[1]

[1]*Department of Respiratory Therapy;* [2]*Department of Exercise Physiology, Bellarmine University, Louisville 40205, KY, USA*

Abstract: In this study, two proposed scales of nicotine dependence were compared: self-administered nicotine intake and acute heart rate sensitivity to smoking. Our aim was to determine if these nicotine dependence scales would rank relative dependence the same in a sample of 15 male chronic smokers who smoked their first cigarette in the morning after overnight abstinence. Heart rate and plasma nicotine levels were measured before and 5, 10, 15, and 30 min after smoking. The results of this pilot study suggest that heart rate sensitivity and nicotine intake do not have a direct linear relationship, but rather a curvilinear relationship. A marked increase in heart rate sensitivity was observed at approximately the 70th percentile of nicotine intake.

Key words: tobacco use disorder; nicotine dependence; nicotine use disorder-classification

尼古丁摄入量和吸烟后急性心率反应预测相同的尼古丁依赖程度?

Jerome F Walker[1,*], Paul D Loprinzi[2], Christy J Kane[1]

贝拉明大学[1]呼吸治疗系；[2]运动生理学系，路易维登 40205，美国

摘 要：本研究采用吸烟摄入尼古丁量和心脏对吸烟的心率敏感性两个测量尼古丁依赖性的量表，比较这两个量表预测尼古丁的依赖性是否相同。15名长期吸烟男性，隔夜禁食后清晨给予第一支香烟，分别测量吸烟前、吸烟后5、10、15和30 min的心率和血液的尼古丁含量。结果显示，心率敏感性和尼古丁摄入量没有直接线性相关，而是曲线关系。心率敏感性在尼古丁摄入量达到70%时有显著增加。

关键词：烟草用量紊乱；尼古丁依赖；尼古丁用量紊乱 -分类
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Cigarette smoking is a leading source of preventable disease and premature death worldwide. Because it is assumed that some smokers are more nicotine dependent than others [1], scaling instruments are needed to assess individual liability [2–4]. Heart rate (HR) sensitivity to smoking after 12 to 24 h of nicotine deprivation has been reported to grade individual differences in nicotine dependence [5], with greater HR response associated with greater dependence [6]. Also associated with nicotine dependence is the Diagnostic and Statistical Manual IV criterion of the need for more nicotine to achieve the desired effect [2]. More dependent smokers obtain higher self-administered nicotine levels [5,7] and greater nicotine reinforcement has been associated with increased withdrawal severity and shorter post-quit attempt relapse time [8]. In this comparison of scales pilot study, HR and plasma nicotine levels were gathered from 15 nicotine-deprived male smokers before and at 5, 10, 15, and 30 min intervals after smoking one cigarette *ad libitum*. The aim of the study was to determine if self-administered nicotine intake and acute HR sensitivity to smoking are parallel measures in ranking nico-

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*Corresponding author. Tel: +1-502-272-8415; FAX: +1-502-272-7602; E-mail: jwalker@bellarmine.edu

tine dependence. We hypothesized that greater nicotine intake would associate with greater HR sensitivity.

1 MATERIALS AND METHODS

Study procedures underwent university Institutional Review Board review prior to data collection. Males having smoked regularly for at least one year were recruited by advertisement placed in the local newspaper. Those interested were scheduled for an initial interview to discuss the purpose and requirements of the study and gave signed consent upon agreeing to enroll. Participants were examined by a physician and excluded from study if there was evidence of any condition known to influence the outcomes (e.g., HR) of the present study, such as cardiopulmonary disease, diabetes mellitus, thyroid dysfunction, or if taking medications known to affect metabolic rate, such as beta-blockers, decongestants, or sedatives. Descriptive and anthropometric data were gathered. The results of the analytic sample are shown in Table 1. On the testing day, participants were instructed not to eat, smoke or drink anything (except water) and to avoid vigorous activity for 12 h prior to testing. This period of smoking deprivation is consistent with other acute nicotine or smoking cardiovascular response studies [9–11].

Daily baseline procedure: Upon arriving to the laboratory at 07: 30 on testing days each participant sat in a comfortable chair for 30 min, during which time alveolar carbon monoxide (CO) was measured (Spirometrics, Inc., Auburn, ME, USA). Values greater than 2.5% were interpreted as the subject had recently smoked, and testing was not continued. Continuous HR was measured by pulse oximeter probe (SensorMedics Corporation, Anaheim, CA, USA). After resting for at least 30 min (or until HR variation was less than 5 beats/min), a 20 gauge stainless steel intravenous catheter (IV) was placed in the dorsal hand or antecubital vein of the arm contralateral to a blood pressure cuff. When HR and blood pressure returned to pre-cannulation levels, a blood sample was collected for baseline plasma nicotine measurement. All plastic ware, glassware, and phlebotomy supplies were kept in a separate room to prevent side stream smoke nicotine contamination. Samples were placed in a refrigerator until the end of the testing day when they were centrifuged, and the plasma frozen at −20 ºC until nicotine assays were performed.

Daily testing procedure: After the daily baseline procedure each participant was allowed 10 min to smoke one machine-measured 0.8 mg nicotine yield cigarette *ad libitum*. Cigarettes were obtained from the Kentucky Tobacco and Health Research Institute, Lexington, KY, USA. While HR was continuously being measured, blood samples for nicotine assay were collected 5, 10, 15, and 30 min after smoking.

Plasma assay procedure: Nicotine concentrations in plasma were determined by gas chromatography (GC) with nitrogen-selective detection. One mL samples containing quinoline (internal standard) were extracted by a three-step liquid-liquid partitioning procedure that manipulated media pH to isolate organic bases. Final extracts were injected into a Hewlett Packard Model 5890 GC containing a 30 m × 32 mm inner diameter DB-Wax column (J & W Scientific). Injections were made in splittless mode, with an initial oven temperature of 100 ºC at a rate of 30 °C/min. These conditions gave retention times of 4.5 and 4.9 min for nicotine and quinoline, respectively. Chromatographic peaks were recorded and integrated using a Hewlett Packard Model 3396 integrator. Relative responses (peak heights) were linear over the range investigated. Coefficients of variation for standard determinations averaged 5%.

Statistical analysis: Mean differences in HR and nicotine levels across the different time periods were examined by repeated measures analysis of variance with Bonferroni *post-hoc* comparisons. Beyond probability testing, the magnitude of each ANOVA-derived F-value was estimated using partial eta-squared, with values ≥ 0.1, 0.3, and 0.5, corresponding with small, medium, and large effects. Regression analysis was then applied to examine the association between HR sensitivity and nicotine intake.

HR sensitivity was calculated as the area under the curve (AUC) of repeated measures HR increase 30 min after smoking in reference to pre-smoking or baseline HR (AUC-HR 30 min) [12]. Self-administered nicotine dose was estimated based on plasma nicotine area under the curve procedures described by Benowitz and others [13]. Repeated measures of plasma nicotine level increase 30 min after smoking were referenced against the pre-smoking value. Correction was made to take into account the terminal half-life beyond the last measured nicotine concentration. Then the dose of nicotine taken systemically from the cigarette was estimated as the product of AUC and population averaged nicotine clearance in males, 16.7 mL • min^{-1} • kg^{-1}. Because HR sensitivity and nicotine intake were polynomial rather

than linear in association, a quadratic regression model was employed. Statistical significance was established at a nominal alpha value less than 0.05.

2 RESULTS

In Table 1 are the descriptive characteristics of the smokers in this study.

HR and plasma nicotine measures before and after smoking are seen in Table 2. HR peaked at 5 min and remained significantly elevated 15 min after smoking, $F(1,14) = 16.012$, $P < 0.002$, partial eta squared = 0.853. Plasma nicotine also peaked at 5 min after smoking and remained significantly elevated throughout the 30 min measurement period: $F(1,14) = 19.504$, $P < 0.001$, partial eta squared = 0.876.

Mean (SD) acute HR sensitivity to smoking (AUC-HR 30 min) was 215.06 (110) beats and nicotine intake was 1.3 (0.44) mg. The dose-response relationship was best fitted using quadratic model curve estimation regression analysis ($R = 0.871$, $R^2 = 0.758$, $P = 0.009$). A strong curvilinear dose-response relationship was observed (Fig. 1). AUC-HR 30 min remained fairly constant across nicotine intake levels up to 1.5 mg and approximately doubled at higher intakes. Thus nicotine intake and AUC-HR 30 min were not parallel in ranking the smokers in the same order of nicotine dependence.

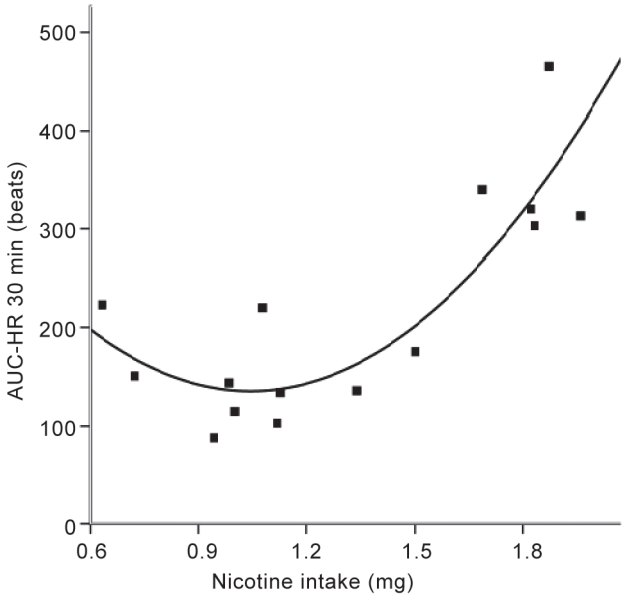

Fig. 1. Nicotine intake and AUC-HR 30 min after smoking fitted by quadratic curve estimation. AUC-HR 30 min: the area under the curve of repeated measures HR increase 30 min after smoking in reference to pre-smoking or baseline HR. $R = 0.871$, $R^2 = 0.758$, $P = 0.009$.

Table 1. Characteristics of the smokers included in the study

	Minimum	Maximum	Mean (SD)
Age (years)	35	58	45.7 (6.5)
Pack-year smoking	2.3	88.0	38.6 (24.4)
%body fat*	15.0	40.4	30.32 (7.0)
Weight (kg)	67.0	122.7	87.5 (14.8)
W/H ratio+	0.91	1.14	1.01 (0.07)

* %body fat was determined by skinfold measurement [14]. + W/H is waist-to-hip ratio.

Table 2. Heart rate and plasma nicotine levels before and after smoking

	Heart rate (beats/min)	Plasma nicotine (ng/mL)
Pre-smoking baseline	64.6 (8.5)	2.53 (2.53)
Post-smoking		
5 min (Peak)	75.6 (10.2)*	21.22 (8.56)+
10 min	73.6 (10.6)*	17.22 (7.00)+
15 min	71.6 (11.1)*	12.93 (5.86)+
30 min	67.3 (9.3)	10.49 (5.81)+

Values are Mean (SD). * Post-smoking HR greater than baseline, $P < 0.002$; + Post-smoking plasma nicotine greater than baseline, $P < 0.001$.

There was no significant mean difference in age, weight, %body fat, pack-year smoking history, or pre-smoking HR in smokers having nicotine intakes greater or less than 1.5 mg. This suggests that individual differences with respect to demographic and anthropometric characteristics do not influence the relationship between nicotine intake and HR sensitivity.

3 DISCUSSION

The effect of nicotine dependence is exceedingly strong. Every year roughly half of all smokers attempt to quit yet only 3% remain nonsmokers for 1 year or longer [1]. Higher quit rates reported in the literature are typically based on follow-up at less than one year and on self-reported smoking status that is not biologically confirmed (by blood or exhaled CO, plasma nicotine, urine cotinine, or other analytic measure). Although there is little evidence of chronic tolerance to the cardiovascular effects of nicotine [9], more dependent smokers obtain higher self-administered nicotine levels and are reported to show greater acute HR increase in response to the first cigarette of the day [6, 13]. Their

withdrawal symptoms also worsen when smoking is withheld [15].

Here we observed a strong dose-response relationship between self-administered nicotine intake and HR sensitivity 30 min after smoking. However, at approximately the 70th percentile of nicotine intake, a two-level rather than continuous HR response was seen. These findings suggest that scaling relative nicotine dependence may be problematic using these two physiologic measures.

The study's limitations include that only male smokers were evaluated. It is possible that the results may have been different if both genders were included or if only females were examined, as previous studies have demonstrated gender differences in nicotine responses [16]. Additionally, the relatively small sample size limits generalizability; however, the findings were not influenced by various male demographic and anthropometric characteristics. This suggests the results may be similar in males of other profile characteristics, for example, those with different pack-year smoking history. Despite the noted limitations, strengths of this pilot study include the demonstration of a non-linear relationship between HR sensitivity and self-administered nicotine intake.

We conclude that acute HR response to smoking is not a linear function of nicotine intake. Rather there appears to be two dose-response levels. Assuming nicotine dependence falls along a continuum and less dependent smokers are more able to quit, scaling relative nicotine dependence may be problematic using these two physiologic measures. Future studies in a larger sample size are needed to confirm these findings. Additionally, future studies examining whether gender influences the relationship between HR sensitivity and self-administered nicotine intake are warranted.

REFERENCES

1 Benowitz NL. Nicotine addiction. N Engl J Med 2010; 362(24): 2295–2303.

2 DiFranza J, Ursprung WW, Lauzon B, Bancej C, Wellman RJ, Ziedonis D, Kim SS, Gervais A, Meltzer B, McKay CE, O'Loughlin J, Okoli CT, Fortuna LR, Tremblay M. A systematic review of the Diagnostic and Statistical Manual diagnostic criteria for nicotine dependence. Addict Behav 2010; 35(5): 373–382.

3 Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The fagerstrom test for nicotine dependence: a revision of the fagerstrom tolerance questionnaire. Br J Addict 1991; 86(9): 1119–1127.

4 Hendricks PS, Prochaska JJ, Humfleet GL, Hall SM. Evaluating the validities of different DSM-IV-based conceptual constructs of tobacco dependence. Addiction 2008; 103(7): 1215–1223.

5 Pomerleau OF, Collins AC, Shiffman S, Pomerleau CS. Why some people smoke and others do not: new perspectives. J Consult Clin Psychol 1993; 61(5): 723–731.

6 Pomerleau OF. Individual differences in sensitivity to nicotine: implications for genetic research on nicotine dependence. Behav Genet 1995; 25(2): 161–177.

7 Hatsukami DK, Hughes JR, Pickens RW. Blood nicotine, smoke exposure and tobacco withdrawal symptoms. Addict Behav 1985; 10(4): 413–417.

8 Perkins KA, Broge M, Gerlach D, Sanders M, Grobe JE, Cherry C, Wilson AS. Acute nicotine reinforcement, but not chronic tolerance, predicts withdrawal and relapse after quitting smoking. Health Psychol 2002; 21(4): 332–339.

9 Perkins KA, Grobe JE, Fonte C, Goettler J, Caggiula AR, Reynolds WA, Stiller RL, Scierka A, Jacob RG. Chronic and acute tolerance to subjective, behavioral and cardiovascular effects of nicotine in humans. J Pharmacol Exp Ther 1994; 270(2): 628–638.

10 Benowitz NL, Jacob P 3rd, Jones RT, Rosenberg J. Interindividual variability in the metabolism and cardiovascular effects of nicotine in man. J Pharmacol Exp Ther 1982; 221(2): 368–372.

11 Niaura R, Shadel WG, Goldstein MG, Hutchinson KE, Abrams DB. Individual differences in responses to the first cigarette following overnight abstinence in regular smokers. Nicotine Tob Res 2001; 3(1): 37–44.

12 Pruessner JC, Kirschbaum C, Meinlschmid G, Hellhammer DH. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinology 2003; 28(7): 916–931.

13 Benowitz NL, Jacob P, III, Herrera B. Nicotine intake and dose response when smoking reduced-nicotine content cigarettes. Clin Pharmacol Ther 2006; 80(6): 703–714.

14 Jackson AS, Pollock ML. Factor analysis and multivariate scaling of anthropometric variables for the assessment of body composition. Med Sci Sports 1976; 8(3): 196–203.

15 West RJ, Russell MA. Cardiovascular and subjective effects of smoking before and after 24 h of abstinence from cigarettes. Psychopharmacology (Berl) 1987; 92(1): 118–121.

16 Perkins KA. Sex differences in nicotine reinforcement and reward: influences on the persistence of tobacco smoking. Nebr Symp Motiv 2009; 55: 143–169.