Nicotine Acutely Inhibits Erectile Tumescence by Altering Heart Rate Variability

Christopher B. Harte

OBJECTIVE To examine potential mechanisms underlying nicotine's effects on male sexual arousal by exploring the mediating role of heart rate variability (HRV).

METHODS The sample comprised 22 healthy, nicotine-naïve men (mean age = 20.91 years; standard deviation = 2.43). Data were taken from a double-blind, randomized, placebo-controlled, crossover trial previously completed and published elsewhere. During each laboratory visit, time-domain parameters of HRV (standard deviation of normal-to-normal [NN] intervals, square root of the mean squared difference of successive NN intervals, and percent of NN intervals for which successive heartbeat intervals differed by at least 50 ms [pNN50]) along with the objective (via penile plethysmography) and subjective indices of sexual arousal were assessed.

RESULTS Acute nicotine ingestion (compared with placebo) was associated with dysregulated sympathovagal balance, which in turn was related to relatively reduced erectile tumescence. HRV did not mediate relations between nicotine intake and self-reported indices of sexual arousal.

CONCLUSION HRV mediated the association between nicotine ingestion and erectile capacity. Findings suggest that dysfunctional cardiac autonomic tone may be an underlying mechanism by which nicotine exerts its deleterious effects on erectile health. UROLOGY 83: 1093–1098, 2014. Published by Elsevier Inc.

Epidemiologic studies indicate that cigarette smokers are at increased risk for erectile dysfunction (ED) compared with nonsmokers.[1,2] Moreover, laboratory investigations have shown that cigarette consumption among chronic smokers[3] and ingestion of isolated nicotine (eg, nicotine gum) among nonsmokers[4] acutely reduce sexual arousal. This relationship also holds in the reverse direction; quitting smoking appears to promote improvements in erectile function.[5,6]

Mechanisms by which tobacco/nicotine may affect erectile physiology remain relatively underexplored. Cigarette smoking may adversely impact penile hemodynamics via central[7] or biochemical[8] mechanisms and peripherally[9] via changes in heart rate variability (HRV). HRV is a way to noninvasively assess vagal cardiac tone and reflects the level of variability from mean heart rate across time. Low levels of HRV (sympathetic nervous system dominance, characterized by low interbeat variability) leaves the heart vulnerable to arrhythmia and sudden death. Conversely, high levels of HRV (parasympathetic nervous system dominance, evidenced by high variability of interbeat intervals) represent healthy cardiac function.

A growing body of literature has begun to explore the inter-relations among cardiac autonomic function, tobacco use, and erectile health. It has been shown that acute nicotine intake impairs HRV,[10] whereas cessation of nicotine improves HRV.[11,12] Furthermore, HRV has been implicated in erectile function.[13] Specifically, individuals with ED have been shown to display dysregulated HRV, indicative of impaired cardiac autonomic regulation (ie, sympathetic hyperactivity).[14,15] Moreover, smoking, HRV, and erectile health may all be interrelated; longitudinal[16] and cross-sectional studies[17] indicate that HRV mediates the relationship between smoking status and/or smoking intensity and erectile tumescence. These findings highlight the possible underlying role of cardiac autonomic function in the physiology of erection and point toward a possible mechanism that explains the link between tobacco use and ED.

In an attempt to explore potential mechanisms underlying tobacco's effects on penile erection, this study examined the mediating role of cardiac autonomic function (assessed via HRV) among a sample of young, healthy, nonsmoking men from the United States without a history of cardiovascular disease (CVD) or myocardial infarct (MI). HRV was chosen as a potential mediator, given that this parameter is a marker of sympathovagal balance, which is a chief underlying mechanism of erectile response (ie, parasympathetic dominance is proerectile, whereas sympathetic dominance is anti-erectile). It was hypothesized that acute nicotine administration (compared with placebo) would be

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From the Research Service, VA Boston Healthcare System, Boston, MA; and the Department of Psychiatry, Boston University School of Medicine, Boston, MA

Reprint requests: Christopher B. Harte, Ph.D., Research Service, VA Boston Healthcare System, 150 S. Huntington Avenue (116-B4), Boston, MA 02130. E-mail: christopher.harte@va.gov

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associated with dysregulation of HRV, which in turn would be associated with reductions in erectile response.

MATERIALS AND METHODS

Participants

Participants were 22 men recruited from an undergraduate psychology subject pool and via community and online advertisements between 2006 and 2007. Participants in the current report were selected from an experiment previously completed and published elsewhere.[4] Inclusion criteria comprised being aged between 18 and 30 years, being currently sexually active, reporting a heterosexual sexual identity, reporting no more than 100 direct lifetime exposures to nicotine, and reporting healthy erectile function (scoring ≥26 on the Erectile Function domain of the International Index of Erectile Function [IIEF][18,19]). Exclusion criteria were as follows: (1) current medication use or medical conditions known to affect sexual functioning; (2) history of treatment for sexual dysfunction; (3) presence of a sexually transmitted infection; (4) an active psychiatric condition; (5) a known allergy to nicotine; (6) current medication use that would adversely interact with nicotine (eg, bupropion, varenicline); (7) a current medical condition that could make nicotine administration unsafe (eg, history of MI, stroke, cardiac dysrythmias); (8) conditions that would interfere with nicotine gum administration (eg, jaw/chewing problems, bridgework, dentures); and (9) history of CVD.

Procedure

A detailed description of experimental procedures can be found elsewhere.[4] In brief, during the first experimental session, self-report (eg, sociodemographic information, medical, sexual, alcohol, and tobacco use history, and erectile function), cardiovascular (systolic and diastolic blood pressures [BP]), and anthropometric (height and weight) data were first collected. Participants were then randomized to receive either nicotine (6 mg) or placebo, both administered double blind in gum form*. Participants were then instructed to measure their flaccid penile circumference (such that they would receive a tailored gauge size), and they were instructed on how to fit the plethysmograph. After a 30-minute waiting period, electrocardiographic (ECG; heart rate [HR], HRV) and sexual response data (resting penile circumference [RPC], erectile tumescence, continuous subjective sexual arousal [SSA]) were collected simultaneously while participants individually viewed audiovisual stimuli. Films consisted of an initial 3-minute nonsexual segment (documentary film presentation), immediately followed by an 8-minute erotic film presentation depicting heterosexual penile-vaginal intercourse. Only ECG data from the initial 3-minute baseline period were examined. The procedures of the second experimental session were identical to the first, and participants were administered the other treatment not received during the first session (nicotine or placebo). After study completion, participants either received credit toward their psychology research requirement or were financially compensated (US $30). All study protocols were approved by the University Institutional Review Board.

Measures

Self-report Survey. Participants completed a survey assessing sociodemographic characteristics, medical history (eg, medical condition(s), current medications), smoking and/or nicotine history (number of direct lifetime exposures, passive tobacco smoke exposure [hours/week]), alcohol use history (number of alcoholic drinks consumed/week), and sexual function (per the IIEF[18]).

Electrocardiography. Autonomic cardiac function was assessed using a 3-channel ECG, and signals were recorded using a Model MP100WS data acquisition unit (BIOPAC Systems, Inc., Santa Barbara, CA) and the software package AcqKnowledge III, Version 3.73 (BIOPAC Systems, Inc.). Normal-to-normal (NN) intervals were collected manually using the AcqKnowledge peak finder function, and artifacts were identified and removed. After cleaning ECG recordings, mean NN interval and mean HR were derived. Kubios HRV Analysis Software (Biosignal Analysis and Medical Imaging Group, University of Kuopio, Kuopio, Finland) was used to calculate time-domain HRV indices. These indices included the standard deviation of NN intervals (SDNN), the square root of the mean squared difference of successive NN intervals (RMSSD), and the percent of NN intervals for which successive heartbeat intervals differed by at least 50 ms (pNN50).

Erectile Responses. Genital responses were assessed via penile plethysmography using a mercury-in-rubber strain gauge (Hokanson, Inc., Bellevue, WA) to capture dynamic changes in penile circumference. Signals were sampled at a rate of 80 samples/second, bandpass filtered (0.5 Hz), digitized (40 Hz), and recorded using a Model MP100WS data acquisition unit and the software package AcqKnowledge III, Version 3.73.

Subjective Sexual Arousal. Continuous SSA was measured during the film presentation using a hand-controlled device, previously shown to be a valid indicator of self-reported sexual arousal.[20] This device consisted of a computer optical mouse mounted on a track divided into 7 equally spaced intervals, where 0 indicated neutral, and 1-7 reflected increasingly higher levels of feeling sexually aroused. The signal was low-pass filtered (0.5 Hz) and digitized (40 Hz), and a software program written in MatLab (The MathWorks, Inc, Natick, MA) transformed the signals into percentage of maximum arousal.

Data Reduction

Erectile responses and SSA scores were computed by averaging all data points within 5-second epochs, and then averaging all epochs within the neutral and erotic film segments. Within-session change scores were calculated for each participant's physiological and SSA recordings by subtracting the value of the mean arousal response throughout the neutral film presentation (sexually unaroused state) from the mean arousal response throughout the erotic film presentation (sexually aroused state). Data were formatted such that they were suitable for a test of statistical mediation. To this end, the experimental condition to which a participant was first assigned was dummy coded (placebo = 0, nicotine = 1). Across-session change scores for the mediator variables (HRV, reflected as SDNN, RMSSD, pNN50) and outcome variables (within-session change in

* One 4-mg nicotine gum piece increases plasma nicotine levels by approximately 8-10 ng/mL within 30 minutes and has a half-life of approximately 120 minutes.[4] Comparatively, a high-yield (0.7-1.2 mg) nicotine cigarette increases plasma nicotine levels by approximately 14 ng/mL within 10 minutes.[4] 6 mg nicotine gum was administered to ensure that a participant's plasma nicotine level would be comparable with smoking one cigarette.