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Hemodynamic and Autonomic Effects of Smokeless Tobacco in Healthy Young Men

Robert Wolk, MD, PHD,* Abu S. M. Shamsuzzaman, MBBS, PHD,* Anna Svatikova, BA,* Christine M. Huyber,* Corey Huck, BA,* Krzysztof Narkiewicz, MD, PHD,† Virend K. Somers, MD, PHD, FACC*

Rochester, Minnesota; and Gdansk, Poland

OBJECTIVES The aim of this study was to investigate the acute hemodynamic and autonomic effects of smokeless tobacco.

BACKGROUND Smokeless tobacco use is increasing. Its cardiovascular effects are not well understood.

METHODS Sixteen healthy, male, habitual snuff tobacco users (aged 22 ± 1 year) were studied, using a randomized, double-blind, placebo-controlled, crossover design with two separate experimental sessions: placebo and tobacco. Muscle sympathetic nerve activity (MSNA), electrocardiogram, blood pressure, calf blood flow, nicotine, and catecholamines were measured.

RESULTS Snuff tobacco increased plasma nicotine from 2.8 ± 0.5 ng/ml to 10.4 ± 1.1 ng/ml. Mean blood pressure increased by 10 ± 1 mm Hg, and heart rate increased by 16 ± 2 beats/min. Peripheral vascular resistance, MSNA, and norepinephrine concentration did not change with tobacco, but epinephrine increased by ~50%.

CONCLUSIONS Oral snuff tobacco increases heart rate, blood pressure, and epinephrine. Despite the increase in blood pressure, there is no decrease in either MSNA or peripheral vascular resistance. Smokeless tobacco is a powerful autonomic and hemodynamic stimulus. Catecholamine release from the adrenal medulla likely contributes to this response. (J Am Coll Cardiol 2005;45:910–4) © 2005 by the American College of Cardiology Foundation

Over 5,000,000 adults and >750,000 adolescents use smokeless tobacco in the U.S. (1). The prevalence is increased in young males, especially athletes (2,3). In contrast to cigarette smoking, the cardiovascular effects of smokeless tobacco are not well understood. Previous studies reported conflicting results regarding cardiovascular risk in persons using smokeless tobacco. Case-control studies suggest no increased risk of myocardial infarction or stroke in regular snuff users (4,5), but a tendency towards increased risk of fatal myocardial infarction (4). A prospective study linked smokeless tobacco to higher risk of cardiovascular death (6), although another study found no association between smokeless tobacco and cardiovascular mortality (7).

Similarly, studies investigating effects of smokeless tobacco on rest blood pressure (BP) (reviewed by Asplund [8]) are inconsistent, noting either an increase (9–12) or no significant change (13) in blood pressure after acute exposure to smokeless tobacco. Many previous studies were not placebo-controlled and/or were not blinded; mechanisms underlying any acute responses to spit tobacco were not investigated.

Effects of chewing tobacco on vascular resistance and sympathetic nerve traffic in humans have never been studied. Using a double-blind, randomized, placebo-controlled, crossover design, we investigated the acute effects of snuff tobacco on heart rate (HR), BP, peripheral vascular resistance, muscle sympathetic nerve activity (MSNA), and catecholamines in healthy male habitual tobacco users.

From the *Mayo Clinic, Rochester, Minnesota; and †Medical University of Gdansk, Gdansk, Poland. Financial support: NIH HL-61560, HL-65176, HL-70302, MO1-RR00585, and 3F05-TW-05200.

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METHODS

Study subjects. We studied 16 healthy, male, habitual spit tobacco users (age 21 ± 1 year; body mass index 27 ± 1 kg/m^2). None of the subjects was taking any medication nor had any chronic disease. All subjects were asked to avoid chewing or smoking tobacco for at least 12 h before each study. The study was approved by the Mayo Clinic Institutional Review Board.

Measurements and procedures. Electrocardiogram was recorded continuously by EKG Bioamplifier (Gould Instrument Systems, Valley View, Ohio). Blood pressure was recorded continuously (Finapres, Ohmeda, Englewood, Colorado) and also measured every minute (Dinamap, Critikon Inc., Tampa, Florida). Calf blood flow was measured by venous occlusion plethysmography (14). Vascular resistance was calculated by dividing mean arterial pressure by flow and is expressed in arbitrary units. Multiunit postganglionic MSNA was recorded from the peroneal nerve with tungsten microelectrodes (15).

Blood samples were drawn at baseline during supine rest, and again after 30 min of tobacco chewing. Plasma nicotine was determined using liquid chromatography tandem mass spectrometry, with interassay variability of 20% at 2 ng/ml, 10% at 5 ng/ml, and 7% at >20 ng/ml. Plasma catecholamines were measured using high-performance liquid

Abbreviations and Acronyms
BP = blood pressure
HR = heart rate
MSNA = muscle sympathetic nerve activity

chromatography (with interassay and intra-assay variability of 3.4% and 3.1%, respectively).

Study protocol. Subjects were studied in the supine position. All measurements were obtained using a randomized, double-blind, placebo-controlled, crossover design with two experimental sessions, a placebo session (Smokey Mountain snuff, Smokey Mountain Chew Inc., Darien, Connecticut), and a tobacco session (Copenhagen moist tobacco snuff, U.S. Tobacco, Nashville, Tennessee). Smokey Mountain and Copenhagen snuff are commercially available tobacco products that are similar in taste, texture, and color, except that Smokey Mountain snuff does not contain tobacco and is nicotine-free. Each session was conducted using the same protocol on two separate days, in a random order.

Baseline measurements were obtained after 10 to 15 min of rest. After the end of baseline recordings, the subjects were given orally 1.5 g of snuff tobacco/placebo for 15 min, followed immediately by the second dose of tobacco/placebo (also 1.5 g), which was then kept in the mouth until the end of the study. The second series of measurements was performed 30 min after the beginning of snuff administration, using exactly the same protocol as at baseline.

Hemodynamic and catecholamine data are reported for 16 subjects in whom measurements were obtained during both sessions. Stable MSNA signals of good technical quality were obtained on both sessions in 10 subjects.

Phenylephrine infusion. Hemodynamic measures and MSNA were also recorded in a separate group of eight healthy subjects (6 males and 2 females; mean age 42 ± 2 years; two subjects were smokers) during phenylephrine infusion in the absence of snuff dipping, in order to mimic the BP responses observed with acute spit tobacco exposure. Phenylephrine was infused in progressively increasing doses to achieve changes in BP similar to those observed after snuff tobacco dipping in the main study cohort of spit tobacco users previously described.

Statistical analysis. Data were analyzed using two-way analysis of variance for repeated-measures with time (before vs. after snuff dipping) as the within factor and session (placebo vs. tobacco) as the between factor. Paired and unpaired (as appropriate) Student *t* tests were also used for comparisons between groups with respect to the change (Δ) in a given variable. A value of $p \leq 0.05$ was considered statistically significant. Data are expressed as mean ± SEM.

RESULTS

Hemodynamic, MSNA, and biochemical measures before and after placebo and tobacco sessions are shown in Table 1. At baseline, all variables were similar before the placebo and the tobacco sessions. Snuff tobacco dipping increased plasma nicotine (from 2.8 ± 0.5 ng/ml to 10.4 ± 1.1 ng/ml; $p < 0.001$), whereas levels remained stable during the placebo session (2.6 ± 0.6 ng/ml vs. 2.7 ± 0.6 ng/ml; p = NS). Furthermore, spit tobacco increased BP and HR (Fig. 1).

Despite the increased BP, both peripheral vascular resistance (Fig. 1) and efferent sympathetic drive to peripheral blood vessels (MSNA) (Fig. 2) were unchanged after tobacco administration. In contrast, a similar increase in BP during phenylephrine infusion (at a dose of 1.06 ± 0.14 μg/kg/min) in healthy subjects in the absence of snuff tobacco dipping caused a marked decrease in HR and MSNA (Figs. 3 and 4).

Plasma norepinephrine concentration remained un-

Table 1. Hemodynamic Parameters, MSNA, and Biochemical Measurements Before and After Placebo and Tobacco Sessions (n = 16)

	Placebo Session		Tobacco Session		Interaction Time × Session
	Before Chewing	After Chewing	Before Chewing	After Chewing	p Value
Hemodynamics					
SBP (mm Hg)	124 ± 2	126 ± 2	122 ± 2	134 ± 2‡	<0.001
DBP (mm Hg)	57 ± 2	60 ± 1†	57 ± 1	64 ± 1‡	<0.001
MAP (mm Hg)	81 ± 2	83 ± 1*	79 ± 1	90 ± 1‡	<0.001
HR (beats/min)	57 ± 1	57 ± 1	57 ± 2	73 ± 2‡	<0.001
PVR (U)	41 ± 5	45 ± 6	44 ± 7	44 ± 6	0.364
MSNA (n = 10) (bursts/min)	23 ± 3	21 ± 4	23 ± 3	20 ± 2	0.768
Biochemical measurements					
Nicotine (ng/ml)	2.6 ± 0.6	2.7 ± 0.6	2.8 ± 0.5	10.4 ± 1.1‡	<0.001
Cotinine (ng/ml)	61 ± 15	59 ± 15	61 ± 19	64 ± 18†	0.001
t-3-OH-cotinine (ng/ml)	39 ± 10	37 ± 9	43 ± 19	44 ± 20	0.212
Norepinephrine (pg/ml)	162 ± 12	172 ± 10	164 ± 17	180 ± 26	0.758
Epinephrine (pg/ml)	18 ± 2	18 ± 2	15 ± 2	23 ± 4*	0.023

*$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$ vs. respective baseline before chewing. The p values in the table were obtained using two-way analysis of variance for repeated measures to evaluate time versus session interactions. The p values marked by symbols were obtained using a paired *t* test to assess changes within each session.

DBP = diastolic blood pressure; HR = heart rate; MAP = mean arterial pressure; MSNA = muscle sympathetic nerve activity; PVR = peripheral vascular resistance; SBP = systolic blood pressure.