Cardiovascular Effects of Tobacco

Hemodynamic and Autonomic Effects of Smokeless Tobacco in Healthy Young Men

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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 smokeless tobacco on heart rate (HR), BP, peripheral vascular resistance, muscle sympathetic nerve activity (MSNA), and catecholamines in healthy male habitual tobacco users.

METHODS

Study subjects. We studied 16 healthy, male, habitual spit tobacco users (age 21 ± 1 year; body mass index 27 ± 1 kg/m²). 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 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
evaluate time versus session interactions. The p values marked by symbols were obtained using a paired *p*/H11005 test.

### Table 1.

<table>
<thead>
<tr>
<th>Hemodynamic Parameters, MSNA, and Biochemical Measurements Before and After Placebo and Tobacco Sessions (n = 16)</th>
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*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.

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

**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-
changed after spit tobacco, but epinephrine levels increased by about 50% (Fig. 2).

**DISCUSSION**

The novel findings of this study are first, that snuff tobacco dipping causes an acute increase in HR and BP; second, that despite the significant BP increase, norepinephrine, peripheral vascular resistance, and efferent sympathetic outflow to muscle resistance vessels are not reduced by acute exposure to spit tobacco; and third, that administration of spit tobacco is associated with a significant increase in plasma epinephrine. These results suggest that the pressor effect of spit tobacco results most likely from an increase in cardiac output. Consistent with this explanation is the observed increase in HR.

Our results suggest the release of epinephrine from the adrenal gland in response to snuff tobacco. Indeed, nicotine evokes catecholamine secretion in adrenal medulla cell cultures (16,17). In dogs whose adrenal glands had been ligated, the pressor response to nicotine was diminished (18). The observed increase in plasma epinephrine speaks to the likelihood of preganglionic sympathetic excitation.

The acute increase in plasma epinephrine with spit tobacco may have implications for both intravascular thrombosis and cardiac arrhythmias. Epinephrine is an important platelet activator and is prothrombogenic; sudden surges in epinephrine may trigger a hypercoagulable state and platelet deposition in damaged arterial wall (19,20). Thus, smokeless tobacco may possibly provide a stimulus for occlusive arterial thrombosis. Epinephrine is also proarrhythmic in animal models and in humans (21); smokeless tobacco may thus conceivably trigger cardiac arrhythmias in susceptible individuals with an arrhythmogenic substrate. Risk for these potential complications may be magnified in the context of significant spit-tobacco-induced increases in BP and HR.

The absence of any significant inhibitory effect of spit tobacco on MSNA (consistent with the lack of any effect on peripheral vascular resistance in the present study) supports the concept of a sympathetic excitatory action of smokeless tobacco. Increasing BP by phenylephrine infusion, to the levels noted after snuff tobacco dipping, activates the baroreflex and elicits profound sympathetic inhibition (Figs. 3 and 4), which would obscure any sympathetic excitatory effects of smokeless tobacco. Therefore, the lack of suppression of MSNA and the increase in HR in the presence of elevated BP, together with the marked increase in epinephrine in response to spit tobacco in our present study, speak further to a potent, spit-tobacco-induced sympathetic excitation.

Several factors may help explain the increase in HR with spit tobacco use despite the BP rise (which would be...
expected to elicit baroreflex-mediated bradycardia). These include nicotine-induced activation of central sympathetic outflow to the heart, and the tachycardic effects of nicotine-induced epinephrine release. Nicotine also has many indirect actions on the heart, including the release of catecholamines from cardiac sympathetic nerve terminals (17).

**Study limitations.** First, we studied the effects of smokeless tobacco only in habitual tobacco users, but we did not
investigate the effects of first acute exposure in nonusers. Nevertheless, the practical applications of our results relate primarily to habitual users of smokeless tobacco.

Second, other mechanisms may explain some of the hemodynamic effects of smokeless tobacco, including high sodium content of smokeless tobacco products (which differs between different brands), as well as the presence of pharmacologically active ingredients other than nicotine (e.g., licorice) (22,23), not measured in the present study.

Conclusions. Oral snuff tobacco leads to acute increases in HR, BP, and plasma epinephrine, in the absence of any reduction of either MSNA or peripheral vascular resistance. Increased epinephrine levels suggest an important role for catecholamine release from the adrenal medulla. These observations suggest that smokeless tobacco is a powerful autonomic and hemodynamic stimulus, with potential implications for cardiac and vascular risk.

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REFERENCES