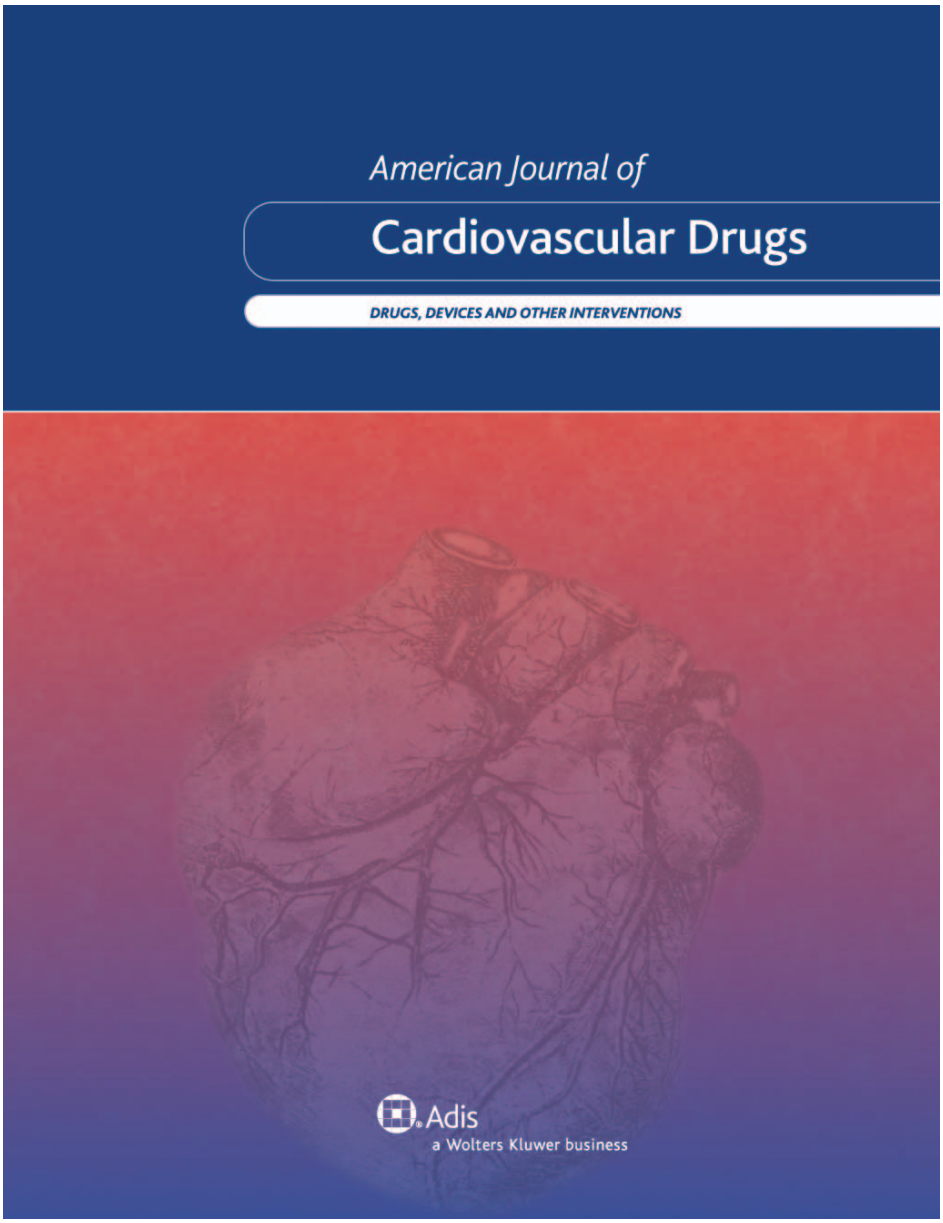

SHORT COMMUNICATION

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Acute Effects of Tobacco Chewing on the Systemic, Pulmonary and Coronary Circulation

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Abstract

Background: Tobacco use is highly prevalent in India, with almost half of adult men consuming tobacco in either smoke or smokeless forms (particularly chewing). Although cigarette smoking is known to produce acute hemodynamic effects, there is a lack of data concerning such effects of chewing tobacco.

Objective: The aim of this study was to determine the acute hemodynamic and coronary vasomotor effects of chewing tobacco.

Methods: Twelve habitual tobacco chewers (mean ± SD age 51.3 ± 6.9 years) undergoing elective coronary angiography were included in the study. Following coronary angiography, a 7F thermodilution Swan Ganz continuous cardiac output pulmonary artery catheter was used to continuously measure the right heart pressures and cardiac output. Having obtained baseline hemodynamic data, 1g of tobacco was given to be chewed. Subsequently, hemodynamic data were obtained periodically over a period of 60 minutes. A repeat left coronary injection was performed, 10 minutes after giving the tobacco, in the right anterior oblique view to estimate the diameter of the left anterior descending (LAD) artery by quantitative coronary angiography.

Results: Chewing tobacco led to a significant acute increase in heart rate (from 68.3 ± 12.4 beats/min to 80.6 ± 14.6 beats/min, peaking at 10 minutes) and cardiac output (from 3.8 ± 0.45 L/min to 4.7 ± 0.64 L/min, peaking at 15 minutes). There were no significant changes in the right atrial, pulmonary artery, or wedge pressures and hence no change in the pulmonary vascular resistance. More importantly, chewing tobacco was associated with coronary vasoconstriction (proximal LAD diameter change from 3.17 ± 0.43 mm to 2.79 ± 0.37 mm; p-value 0.02; mid LAD diameter change from 2.75 ± 0.36 mm to 2.40 ± 0.22 mm; p-value 0.03).

Conclusion: Chewing smokeless tobacco leads to coronary vasoconstriction and also produces significant hemodynamic alterations. These changes may have a bearing on excess vascular disease.

Introduction

Tobacco use is highly prevalent in India, even among the vast rural and lower socioeconomic population. Nearly a third of Indian adult men smoke, while half consume tobacco in either smoking or smokeless forms.[1] Total deaths attributable to tobacco use in India at present are around 700 000 per year.[2] Chewing is the most common form of smokeless tobacco use in India.[1,2] Nicotine is as well absorbed from smokeless tobacco and the levels remain elevated for a longer duration compared with smoking tobacco.[3,4] Most studies indicate that the cardiovascular risk among smokeless tobacco users is lower than among smokers, but is higher than in non-users of tobacco.[3,5,6]

It is well known that the acute and chronic effects are quite variable among different forms of tobacco. Acute hemodynamic studies have documented significant increases in heart rate, BP, and cardiac output following tobacco use in the form of smoking and snuff.[7,8] Cigarette smoking causes acute vasoconstriction of the epicardial coronary arteries[9] and reduces coronary flow reserve.[10] Such study data are not available for chewing tobacco. The objective of this study was to determine the acute hemodynamic and coronary vasomotor effects of chewing tobacco in humans.

Methods

Patient Group

Twelve male patients (mean ± SD age 51.3 ± 6.9 years) were studied during coronary arteriography that was being performed for diagnostic purposes. The mean weight of the included subjects was 57.4 ± 7.3 kg (range 48–72 kg). All vasoactive therapies, including the use of chewing tobacco, were discontinued 48 hours before the study, but aspirin and clopidogrel were continued. The discontinued medications included ACE inhibitors in five patients, β-adrenergic receptor antagonists (β-blockers) in seven patients, and calcium antagonists in four patients. All the patients had been habitual chewers of tobacco for many years, and three patients also smoked cigarettes or bidis. None of the patients had proven obstructive coronary artery disease. Exclusion criteria included women of child-bearing potential, myocardial infarction within 1 month, recent unstable angina or rest angina, uncontrolled hypertension, cardiac arrhythmias, and patients with significant obstructive coronary disease.

The study of a limited number of patients was approved by the Ethics Committee of the All India Institute of Medical Sciences. Each patient was issued with an appropriate information sheet and written informed consent was obtained. The study was conducted according to the recommendations of the Declaration of Helsinki on biomedical research involving human subjects.

Central Hemodynamic Study

Routine left ventriculography and selective coronary arteriography were performed using the conventional Judkins technique.[11] Nitroglycerin was not used routinely. After the diagnostic procedure, the Judkins catheter was retained in the aorta to measure the aortic pressures. A 7F thermodilution Swan Ganz Continuous Cardiac Output (CCO) pulmonary artery catheter (Edwards Lifesciences, Irvine, CA, USA) was positioned in the pulmonary artery and was used to measure the pulmonary artery systolic, diastolic, and occluded wedge pressures. The cardiac output was continuously measured using the Vigilance II CCO monitor (Edwards Lifesciences, Irvine, CA, USA). The Vigilance monitor uses thermal energy emitted by the thermal filament located in the catheter to calculate the cardiac output using thermodilution principles. Hard copies of systemic and pulmonary arterial pressure tracings were obtained at baseline and at 5-minute intervals until reproducible. Thereafter, the measurements were made every 15 minutes following the commencement of tobacco chewing. Heart rate was measured from a continuously monitored ECG, and hard copy ECGs were obtained at the same time points. Cardiac output was continuously measured and a mean value determined from three readings at each time point. The total systemic vascular resistance and the total pulmonary vascular resistance were calculated at baseline and at 15 minutes, 30 minutes, and 60 minutes following the start of tobacco consumption.

Tobacco Administration

Baseline measurements were obtained after a 15-minute rest. Subsequently, smokeless chewing tobacco (1 g of crushed tobacco leaves, *Ravi Brand*™) was given to each subject and retained in the mouth until the end of the study. None of the subjects reported any adverse effects of the tobacco. Measurements were made every 15 minutes up to 60 minutes, at which point the study was terminated. Blood samples were obtained for the determination of serum cotinine levels at 15 and 30 minutes.

Quantitative Coronary Angiography

In all 12 subjects the left anterior descending arteries, which were found to be normal, were studied before and 10 minutes after the start of tobacco consumption. Serial angiograms were obtained using a Siemens Angioscope C arm. The x-ray tube-to-patient distance was fixed to maintain identical magnification and to avoid parallax error. Non-ionic contrast medium 4–7 mL (Omnipaque, GE Healthcare, Cork, Ireland) was injected manually into the coronary artery under study. After visualization of the coronary artery system in the standard views, a projection was chosen that allowed simultaneous visualization of the coronary artery system and the diagnostic 6F catheter that was used for the reference measurement. Diastolic cine frames were selected at comparable points in the cardiac cycle, and computer-assisted quantitative coronary angiography (QCA) analysis (Siemens automated QCA software) was performed by an independent observer in an unblinded manner according to methods described previously.[12] The contours of the selected vessel regions were detected automatically by the computer; the contour data were corrected for pincushion distortion, and the absolute dimensions of the vessel were determined with the use of the coronary catheter for calibration. Several corresponding segments were identified along the length of the artery and three measurements were taken within a distance of 3 mm. The average of the three values was taken to

Table I. Mean ± SD values for central hemodynamic parameters at baseline and after 15, 30, and 60 min of tobacco chewing

Variable	Baseline	15 min	30 min	60 min
Heart rate (beats/min)	68.3 ± 12.4	78.2 ± 15.2[a]	77.1 ± 10.1[a]	76.3 ± 13.8[a]
Cardiac output (L/min)	3.8 ± 0.5	4.7 ± 0.6[a]	4.5 ± 0.7[a]	4.1 ± 0.5[a]
Mean aortic pressure (mmHg)	110.1 ± 15.1	112.9 ± 15.8	111.4 ± 18.1	110.4 ± 15.7
SVR (WU)	27.6 ± 5.3	22.9 ± 3.2[a]	23.2 ± 2.8[a]	25.5 ± 3.5
RA pressure (mmHg)	6.0 ± 2.9	6.1 ± 2.9	6.6 ± 2.7[a]	5.9 ± 2.5
Pulmonary artery pressure (mmHg)	18.2 ± 2.9	18.4 ± 3.6	19.8 ± 6.9	18.3 ± 3.6
PC wedge pressure (mmHg)	12.0 ± 3.9	11.7 ± 4.3	11.9 ± 4.4	12.4 ± 3.6
PVR (WU)	1.6 ± 0.6	1.6 ± 0.7	1.7 ± 0.9	1.4 ± 0.4

a Change statistically significant compared with baseline ($p < 0.01$).

PC = pulmonary capillary; **PVR** = pulmonary vascular resistance; **RA** = right atrial; **SVR** = systemic vascular resistance.

represent the diameter of the segment. The variability of this analysis in our laboratory is similar to that previously reported.[12]

Statistical Analysis

Results are expressed as mean ± standard deviation. The time-bound changes in the different variables were analyzed using ANOVA and the respective p-values were calculated. Statistical significance between individual time points was tested using Bonferroni's test. Statistical analysis was done using the statistical software Stata 9.1 (College Statistix, Tallahassee, FL, USA).

Results

Twelve male patients were studied; two were diabetic, and six were hypertensive. Four patients were included in the study for evaluation of atypical angina with a moderately positive exercise test, while the others were undergoing coronary angiography for chronic stable angina. None of the patients had significant obstructive coronary artery disease (>70% luminal narrowing). The baseline BP was less than 160/90 mmHg in all patients. All patients had an angiographically normal left anterior descending (LAD) coronary artery, which was studied for the effects of chewing tobacco. No serious untoward incident was observed during the study. The median serum cotinine level increased from 3.5 ng/mL at baseline to 107.5 ng/mL at 15 minutes and peaked at 245 ng/mL after 30 minutes of tobacco chewing.

Central Hemodynamics

There was a significant increase in heart rate immediately after the consumption of tobacco, which peaked at 10 minutes, but remained significantly elevated until 60 minutes of consumption. The cardiac output also increased significantly, and the maximum increase was observed at 15 minutes following the start of tobacco consumption (table I, figure 1). There was no significant change in the mean aortic pressure. The rate-pressure product, a measure of myocardial workload, was significantly elevated. There was a significant decrease in systemic vascular resistance. There was no significant change in mean pulmonary artery or pulmonary capillary wedge pressures.

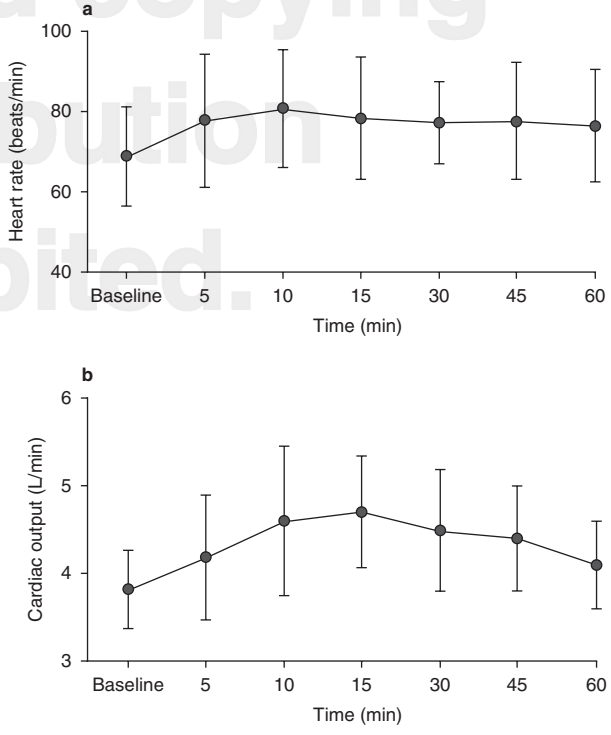

Fig. 1. Acute hemodynamic changes following tobacco chewing. Changes in (**a**) heart rate and (**b**) cardiac output at all time points were statistically significant compared with baseline ($p < 0.01$ at all time points except at 60 minutes when $p < 0.04$).

Table II. Proximal and mid left anterior descending artery (LAD) diameter at baseline and after 10 min of tobacco chewing

Variable	Baseline	10 min	p-Value
Proximal LAD	3.17 ± 0.43	2.79 ± 0.37	0.02
Mid LAD	2.75 ± 0.36	2.40 ± 0.22	0.03
Distal LAD	2.27 ± 0.23	2.15 ± 0.21	0.21

Consequently, there was no significant change in pulmonary vascular resistance (table I).

Coronary Artery Diameters

Chewing tobacco caused a significant reduction in mean absolute coronary diameter from 3.17 ± 0.43 mm to 2.79 ± 0.37 mm (12%; $p < 0.02$) in the proximal and from 2.75 ± 0.36 mm to 2.40 ± 0.22 mm (13%; $p < 0.03$) in the mid segments, respectively, at 10 minutes of tobacco consumption. The change in distal LAD diameter (5%) did not achieve statistical significance (table II). There were no clinical symptoms suggestive of angina or any ECG evidence of myocardial ischemia associated with these changes. No relationship was apparent between the age of the patient and the vasoconstrictive effect of chewing tobacco.

Discussion

In India, smokeless tobacco use is higher among adult men and women than smoking.[13] Smokeless tobacco use was found among 38.1% of men and 9.9% of women, while 33.3% of the men and 1.6% of women smoked.[13] Unlike the chewing of gum, which is a common practice in the Western world, chewing tobacco in India takes the form of dry tobacco leaves with added flavors. Tobacco chewing may represent one of the largest forms of smokeless tobacco use in the world. This acute hemodynamic study has shown that tobacco chewing leads to coronary vasoconstriction, with acute increases in heart rate and cardiac output.

Chewing of tobacco causes acute vasoconstriction of the epicardial coronary arteries, as is seen with smoking.[9] The mechanism behind the reduction in coronary diameter may involve a diffuse hyperactive response to constrictor effects as seen in variant angina. Since the magnitudes of vasoconstriction due to smoking and tobacco chewing are comparable, this effect is likely to be due to nicotine or a common component of tobacco, rather than to smoke or carbon monoxide. Stimulation of coronary artery α-adrenergic receptors by circulating or locally released catecholamines may be responsible for these effects.[14] Acute cigarette smoking leads to temporary endothelial dysfunction and nicotine alone may explain some of the effects.[15] This differentiated rather than generalized vasomotor response to various tobacco products provides an opportunity to dissect the role of individual components among various forms of tobacco.

Tobacco consumption in any form acutely increases the heart rate by an average of 7–19 beats/min, and even the fetal heart rate increases following tobacco use by pregnant women.[7] These effects are related to an increase in the sympathetic and adrenomedullary activity as a result of sympathetic ganglia and adrenal medulla nicotinic receptor activation.[14] Only a few hemodynamic studies have directly measured cardiac output following tobacco consumption. In our study, the mean cardiac output increased by 0.9 L/min and the maximum increase was at 15 minutes following initial tobacco exposure.

Many studies have consistently shown that smoking increases BP.[7] However, the effect of smokeless tobacco on BP is variable. Increases of up to 21 mmHg in systolic BP and 14 mmHg in diastolic BP have been documented with forms of snuff,[8,16] while a few studies have failed to show an increase in BP.[17,18] Population studies investigating the effect of smokeless tobacco on BP are also inconsistent, showing either an increase or no significant change.[19,20] The variability in sodium, nicotine, and licorice content among the various forms of tobacco could explain the variability in BP response.

Smoking and smokeless tobacco use is known to cause peripheral vasoconstriction. Acute cigarette smoking reduces aortic elastic properties, radial artery compliance, and renal, cutaneous, and cerebral blood flow.[21-23] The precise mechanisms for this altered vascular reactivity are complex and are not fully understood. The magnitude of constrictor effects varies with age, presence of hypertension, current smoking, and integrity of endothelial function. In our study, chewing of tobacco resulted in a decrease in total systemic vascular resistance that persisted for 20 minutes. The magnitude of vasodilatation did not vary with the presence of hypertension, diabetes mellitus, or age. This is the first documentation of reduced systemic vascular resistance in humans with the use of any tobacco product, although an earlier study suggested that smoking in healthy subjects acutely increased middle cerebral artery mean flow velocity, suggesting vasodilatation.[24] Furthermore, studies that failed to show an acute increase in BP showed an increase in cardiac output, thereby suggesting a decrease in systemic vascular resistance (SVR), even though SVR was not directly measured in these studies.[3,17] The intense increase in cardiac output with peripheral vasodilatation may explain the intense flushing and giddiness reported commonly among first-time users of chewing tobacco. The flushing is also commonly

noticed among habitual users. The potential ability to cause vasodilatation may be responsible for the less than expected long-term adverse events with smokeless tobacco consumption.

In our study, chewing a small quantity of crushed tobacco leaves (1 g) led to very high levels of cotinine, which suggests that the nicotine content of the Indian form of chewing tobacco is high. It is estimated that Indian smokeless tobacco products for chewing (khaini, zarda, and unprocessed tobacco) tend to contain more nicotine (13.8–65.0 mg/g) than American smokeless tobacco.[25] Hence, the study results may not be generalizable to most of the smokeless tobacco forms available in Sweden and the US. Furthermore, all the patients included in the study had diabetes, hypertension, or suspected coronary disease, and are likely to have had endothelial dysfunction. Hence, the results of altered vasomotor reactivity may not be generalizable to normal healthy users of smokeless tobacco.

The invasive nature of the study and the strict inclusion criteria made it extremely difficult to include a larger number of subjects. The study therefore included only a small number of subjects, but the results are consistent. Only a single dose of 1g of tobacco leaf was given to all participants regardless of body size. The quantity of tobacco used was much less than regularly used (3–5 g), but the study findings were statistically significant even with this low dose. The use of only male patients limits generalizability of the findings to women. We did not estimate the plasma neurohormones, which may be useful in understanding the underlying mechanisms. The timing of repeat angiography chosen in the study (10 minutes) happened to be earlier than the peak increases in heart rate and cardiac output, which could have underestimated the changes in coronary diameter.

Conclusion

Chewing of tobacco in the Indian form leads to coronary vasoconstriction and systemic vasodilatation as seen in our study among a group of Indian male habitual tobacco chewers. It acutely increases heart rate and cardiac output. These hemodynamic and coronary vasomotor changes may underlie the excess vascular disease associated with tobacco chewing. The varying acute cardiovascular effects of smoking and chewing tobacco provide an opportunity to explore the effects of different components of tobacco products in future studies.

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