Electrical Disturbance in Heart by Smokeless Tobacco

Aniket Puri*, Gaurav Chaudhary**, Rohit Srivastava***, Sunita Tiwari****

Abstract
Smokeless tobacco use in the form of chewed tobacco or snuff is common in various parts of the world, including India. It is well known that smokeless tobacco consumption is responsible for cancer but less is known about its role as a risk factor for cardiovascular disease. Nicotine, the main constituent of tobacco smoke is responsible for the elevated risk of the cardiovascular disease and sudden coronary death associated with smoking, presumably by provoking cardiac arrhythmias. This review discusses some of the acute and chronic cardiac effects of smokeless tobacco on cardiovascular disease with special reference to the electrical disturbance as well as comparing nicotine kinetics between smoking and smokeless tobacco. It would further enhance the clamor to urge people to quit all forms of tobacco consumption.

Introduction

Globally the use of smokeless tobacco has gained popularity. Smoking has declined consistently over the last 30 years due to the vigorous efforts toward increasing awareness of the adverse effects of smoking. Paradoxically, smokeless tobacco has increased its has made resurgence in the United States and other developed nations since the 1970s. Smokeless tobacco is mainly used orally, and nasal use is less common.1 Chewed tobacco and snuff are the two major types of smokeless tobacco even in India. Within these groups there are several types of chewed tobacco differentiated by formulations. In India there is a unique presence to use of chewed tobacco both in males and females. Adverse cardiovascular effects of smoking are well known, but the hazards of smokeless tobacco are less well known. This article is an effort to unearth various issues, acute and chronic influence of tobacco usage and cardiovascular disease with special reference to the electrical disturbance in heart by smokeless tobacco.

The Burden of the Problem

The Countries in South Asia are major producers of tobacco and the region is a major exporter, with India being the leader. Current production figures are shown in Table 1. In south Asian countries like India smokeless tobacco is available in various forms i.e. khaini, zarda, gutka etc. and various forms of smokeless tobacco are chewed, sucked or applied to teeth.

Table 1 : Tobacco production in selected countries

<table>
<thead>
<tr>
<th>Major Producing countries</th>
<th>Production (metric tonnes) of tobacco leaves</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Asian region</td>
<td></td>
</tr>
<tr>
<td>Bangladesh</td>
<td>370000†</td>
</tr>
<tr>
<td>India</td>
<td>575000†</td>
</tr>
<tr>
<td>Pakistan</td>
<td>85100†</td>
</tr>
<tr>
<td>World</td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>654250</td>
</tr>
<tr>
<td>China</td>
<td>2400000†</td>
</tr>
<tr>
<td>USA</td>
<td>401890</td>
</tr>
</tbody>
</table>

*FAO estimated; †unofficial figure

Table 2 : Nicotine content of cigarettes and smokeless tobacco

<table>
<thead>
<tr>
<th>Concentration of Nicotine (mg/g)</th>
<th>Typical Single Dose (g Tobacco)</th>
<th>Nicotine in Single Dose (mg)</th>
<th>Nicotine in Dose Typically consumed in 1 day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarettes (15)</td>
<td>15.7 (13.3-26.9)</td>
<td>0.54</td>
<td>8.4 (168 mg per 20 cigarettes)</td>
</tr>
<tr>
<td>Moist snuff (8)</td>
<td>10.5 (6.1-16.6)</td>
<td>1.4 (14.5 mg per 15 mg)</td>
<td></td>
</tr>
<tr>
<td>Chewing tobacco (2)</td>
<td>16.8 (8.1-24.5)</td>
<td>7.9 (133.0 mg per 70 g)</td>
<td></td>
</tr>
</tbody>
</table>

*Number of brand tested; †Range.

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concentrations of nicotine are shown in Table 2.

Nicotine Kinetics in Smoking and Smokeless Tobacco

Nicotine blood levels differ over time following use of various tobacco products. Blood or plasma nicotine concentrations sampled in the afternoon in smokers generally range from 10 to 50 ng/ml. Typical trough concentrations during daily smoking are 10 to 37 ng/ml, and typical peak concentrations range between 19 and 50 ng/ml. The increment in venous blood nicotine concentration after smoking a single cigarette ranges from 5 to 30 ng/ml, depending on how a cigarette is smoked. In a recent study, the mean nicotine boost after smoking a cigarette was 10.9 ng/ml in smokers with no smoking abstinence on the study day. In a study it was found that the nicotine content of six tobacco products, Bandits Wintergreen) to 7.5 for three Skoal Long Cut brands to 11.4 mg/g (Copenhagen Snuff). Nicotine most readily crosses the oral mucosa when it is in its un-ionized form. The degree to which nicotine is present in this form is a function of the pH of the tobacco; at higher pH levels (more alkaline), nicotine is un-ionized. They demonstrated that because the pH levels of the six tobacco products ranged from 6.9 (Skoal Bandits Wintergreen) to 7.5 for three Skoal Long Cut brands to 8.6 (Copenhagen Snuff), the amount of free (un-ionized) nicotine in solution ranged from 0.53 mg/g to 9.03 mg/g, respectively—a 17-fold difference in nicotine yield.

Tachycardiac Effect of Smokeless Tobacco

The hemodynamic effects of smokeless tobacco appear to be mediated by nicotine. Nicotine works primarily by enhancing the release of various neurotransmitters, including epinephrine, norepinephrine, dopamine, acetylcholine, serotonin, vasopressin, glutamate, NO, calcitonin growth-related peptide (CGRP) and beta-endorphin. Nicotine acts on nicotinic cholinergic receptor located in the brain, autonomic ganglia, the adrenal and neuromuscular junction and provokes the release of epinephrine.

Various hemodynamic effects of smokeless tobacco have been studied. A Recent study, on this topic revealed, that snuff tobacco cause an acute increase in heart rate (HR) and blood pressure (BP); secondly, despite the significant increase in blood pressure, norepinephrine, peripheral vascular resistance, and effenter sympathetic outflow to muscle resistance vessels are not reduced by acute exposure to spit tobacco; and lastly that administration of spit tobacco is associated with a significant increase in plasma epinephrine. These results suggest that the pressure effect of spit tobacco result most likely from an increase in cardiac output. Consistent with this explanation is the observed increase in HR. These results also suggest the release of epinephrine from the adrenal gland in response to spit tobacco. Indeed, nicotine evokes catecholamine secretion in adrenal medulla cell cultures. 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. Thus, smokeless tobacco may possibly provide a stimulus for occlusive arterial thrombosis. Epinephrine is also proarhythmic in animal models and in humans; 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 (muscle sympathetic nerve activity) supports the concept of a sympathetic excitatory action of smokeless tobacco. Increasing BP by phenylephrine infusion, to the levels noted after sniff tobacco dipping, activates the baroreflex and elicits profound sympathetic inhibition 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 the 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. 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. Nicotine acts as a sympathomimetic drug to increase heart rate, BP, and cardiac contractility and to constrict some blood vessels. Adverse Health consequences of Nicotine have been summarized in Table 3.

Bradydynamia Effect of Smokeless Tobacco

Nicotine is also implicated in a wide spectrum of cardiac rhythm disorder, including transient sinus arrest, SA block, AV block, atrial and ventricular tachyarrhythmia. It has been suggested that Kv4.3 and Kv4.2 are the major molecular constituents of native cardiac. The ability of nicotine to block Kv4.3 and Kv4.2 might contribute to the previously observed lengthening of cardiac APD in many preparations . Nicotine preferentially prolongs initial repolarization and the subsequent plateau phases, consistent with the participation of Ito in early phases of repolarization. Thus nicotine in smokeless tobacco can be considered a major risk for sinus node dysfunction and various other rhythm disturbances.
Table 3: Adverse health consequences of nicotine in human

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>Metabolic</th>
<th>Central nervous system</th>
<th>Endocrine</th>
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<tbody>
<tr>
<td>Increase heart rate</td>
<td>Increase free fatty acid</td>
<td>Arousal or relaxation</td>
<td>Increase growth hormone</td>
</tr>
<tr>
<td>Cardiac contractile</td>
<td>Glycerol</td>
<td>Electroencephalographic change</td>
<td>Vasopressin</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Lactate</td>
<td>Tremor</td>
<td>Beta endorphins</td>
</tr>
<tr>
<td>Cutaneous release</td>
<td></td>
<td></td>
<td>Inhibition of prostacyclin synthesis</td>
</tr>
</tbody>
</table>

One study performed a detailed work on effect of nicotine on Kv 4.3 and Kv 4.2 channels levels expressed in xenopus/Oynes were studied at whole cell and signal channel levels, the effect of nicotine on transient outward K+ current (Ito) were studied by use of whole cell patch clamp technique in canine ventricular myocytes. Nicotine potentially inhibited Kv4 current of total inhibition of Kv 4.3 and (Ito) by nicotine, 40% was due to tonic block and 60% attributable to use dependent block. Nicotine reduced single channel conductance, open probabilities and open time, but increased the closed time of Kv 4.3. The nicotine effect was not altered by various neurotransmitter receptors indicating direct effect on (Ito) channels.23

Thus molecular evidence of nicotine electrophysiology has shown nicotine a potent inhibitor of cardiac-A type K+ channels. This action may contribute to the ability of nicotine to affect the cardiac electrophysiology.

Conclusion

The use of smokeless tobacco is common in many parts of the world and increasing day by day and various studies on the effect of smokeless tobacco suggest that there is an association between smokeless tobacco use and adverse cardiovascular risk.

Smokeless tobacco leads to acute increases in heart rate, blood pressure and plasma epinephrine. These observations suggest that smokeless tobacco is a powerful autonomic and hemodynamic stimulus, with potential implications for cardiovascular risk. Nicotine in smokeless tobacco gives rise to strong physical dependence similar to smoking. In comparison to smoking, the evidence on health risks related to smokeless tobacco use is relatively limited especially in relation to the electrical distribution of heart.

Effects on the cardiovascular system, such as sinus node dysfunction and AV node dysfunction are potentially of great public health importance. Unfortunately, available evidence is inconclusive, and further studies are needed to look at the role of smokeless tobacco as a causal factor for various electrical disturbances in the heart. Given this and other health risks associated with smokeless tobacco use, all current users should be counseled to quit using smokeless tobacco.

Abbreviations

Ito: Transient outward K+ current
HR: Heart Rate
BP: Blood Pressure
MSNA: Muscle Sympathetic Nerve Activity

References