Original Article

Acute Effects of Chewing Tobacco on Coronary Microcirculation and Hemodynamics in Habitual Tobacco Chewers

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Abstract

Background: Long-term adverse cardiovascular effects of smokeless tobacco are well established, however, the effect of chewing tobacco on coronary microcirculation and hemodynamic have not been studied. We intended to analyze the acute effect of chewing tobacco on coronary microcirculation and hemodynamics in habitual tobacco chewers with stable coronary artery disease undergoing elective percutaneous coronary intervention (PCI). **Materials and Methods:** We prospectively enrolled seven habitual tobacco chewers with stable coronary artery disease with single vessel disease or double vessel disease satisfying the criteria for elective PCI. Patients were instructed to keep 1 g of crushed dried tobacco leaves in the mouth after a successful PCI. Lesion in last stented vessels was evaluated for fractional flow reserve (FFR), coronary flow reserve (CFR), and index of microcirculatory resistance (IMR) post-PCI, after 15 min and 30 min of tobacco chewing along with the measurement of serum cotinine levels. **Results:** Oral tobacco led to high levels of cotinine in the majority of patients. There was an insignificant rise in heart rate, systolic and diastolic blood pressure following tobacco consumption. Baseline CFR (median 1.6, range 1.1–5.5) was low in tobacco chewers after PCI even after optimum FFR (0.9 ± 0.05) in the majority of patients suggesting abnormal microvascular hemodynamics (high IMR in 3 patients, overall median 14.2, range 7–36.2). However, there was no significant change in the estimated CFR or IMR values following tobacco chewing. One patient had bradycardia and hypotension which may be related to vagal reaction or acute nicotine poisoning. **Conclusion:** Tobacco chewers have abnormal coronary microcirculation hemodynamics even following a successful PCI. However, the coronary micocirculation and hemodynamics do not change acutely following tobacco chewing despite high serum cotinine concentrations.

Key words: Coronary flow reserve, cotinine, fractional flow reserve, index of microcirculatory resistance, oral tobacco

Introduction

Tobacco consumption is reported to be the leading preventable cause of death worldwide, and it currently causes 5.4 million deaths/year.[1] Smokeless tobacco use is high in countries of South and Southeast Asia, Africa, and Northern Europe.[2] Chewing is the most common form of smokeless tobacco use in India.[3-5] Smokeless tobacco consistently produces the levels of nicotine higher than those seen with smoking and causes similar sympathetic neural stimulation and acute cardiovascular effects.[6,7] The long-term adverse cardiovascular effects of smokeless tobacco use are suggested to be less than those caused by smoking, but are more than those found in nonusers.[6-11] However, a few studies suggest that chewing tobacco is associated with similar cardiovascular risk as smoking.[12] The acute effects of chewing tobacco on coronary microcirculation have not been studied. We intended to study the acute effects of chewing tobacco on the coronary microcirculation, quantified by measuring fractional flow reserve (FFR), coronary flow reserve (CFR), coronary velocity flow reserve, and index of microcirculatory resistance (IMR) before and after tobacco use, along with effects on other hemodynamic parameters.

Materials and Methods

All chronic tobacco chewers aged 25–75 years, with stable coronary artery disease undergoing elective percutaneous

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coronary interventions (PCIs) satisfying the inclusion criteria and giving written informed consent were included in this study. Patients who chewed tobacco occasionally, less than once per month were considered nontobacco users for the study purpose. Patients who were presently active smokers of any tobacco product were excluded. Those occasional smokers, less than once per month were considered as nonsmokers and were included in this study provided that they had last smoked at least 3 months earlier. Patients with recent myocardial infarction of <1-month, and patients presenting with acute coronary syndromes (UA/non-ST elevation myocardial infarction [NSTEMI] or rest angina), patients found to have insignificant coronary artery disease on angiography (<50% stenosis) or diffuse coronary lesions, patients diagnosed as triple vessel disease or left main disease and who meet the criteria for coronary artery bypass grafting according to the present American Heart Association (AHA)/American College of Cardiology (ACC) guidelines were excluded. Women of child bearing potential, significant comorbidities, contraindications to dual antiplatelet use, and history contrast allergy were the other exclusions. The study was approved by the Institute's Ethics Committee.

Seven patients were recruited over a period of 2 years. Detailed history and examination were done on each patient. All the patients underwent a routine electrocardiogram (ECG), echocardiography, and blood tests. Patients with documented chronic stable angina meeting criteria for elective coronary interventions on the basis of present ACC/AHA guidelines were taken up for a coronary angiography. All patients would be counseled about quitting tobacco products preferably from the day of their first visit, but they had completely abstained from tobacco products at least 1-day before the day of coronary angiography.

Cardiac hemodynamic study

Selective coronary arteriography was performed using the conventional Judkins technique, and PCI was performed with standard institutional protocols. Baseline measurements were obtained after a 15 min rest. Subsequently, smokeless chewing tobacco (1 g of crushed tobacco leaves covered in porous filter paper used in tea-bags for uniform absorption and to avoid unpleasant taste of tobacco) were given to each subject and retained in the mouth until the end of the study. Measurements were made every 15 min until 30 min at which point the study is to be terminated. Blood samples for serum cotinine levels were obtained at baseline, 15 min, and 30 min. Heart rate and blood pressure were measured from a continuously monitored ECG and arterial pressure line at baseline, 15 min, and 30 min following tobacco consumption.

FFR was measured using high fidelity intracoronary pressure wire RadiAnalyzer express® (Radi Medical Systems AB Palmbladsgatan, Sweden). The post-PCI segment was imaged in the best profiled view. After calibrating the sensor, the wire was positioned at the tip of guiding catheter. With the guiding catheter in aorta, equal pressures (defined as <5 mm Hg difference) in wire sensor and aorta were confirmed. The intracoronary pressure wire was then advanced. Maximal hyperemia was induced using intravenous adenosine administered through the femoral vein at a rate of 140/ug/kg/min. FFR, CFR, and IMR were calculated at maximal hyperemia. The dose of adenosine used in basal condition was directly given while calculating FFR, CFR, and IMR posttobacco chewing, so as to prevent any error in measuring these parameters due to dose effect. CFR was measured by thermo dilution principle which measures the coronary blood flow by measuring the temperature fall between the shaft and the tip of thermister catheter. This measure also provides us the mean transit time (Tm), which is required to calculate IMR.

FFR = Pd/Pa (Pd = pressure distal to stenosis, Pa = aortic pressure).

CFR = Qh/Qb (Qh = hyperemic cerebral blood flow [CBF], Qb = basal CBF).

IMR = Pd × Tm (Pd = pressure distal to stenosis, Tm = mean transit time).

FFR recording was done at baseline and then at 15 min and 30 min after tobacco chewing. During the duration of 30 min, the guiding catheter and the pressure wire were withdrawn to the aorta, and were regularly flushed. During the whole procedure, heparin was given to maintain an activated clotting time >250. In case of double vessel disease, the lesion in last stented vessels was evaluated for FFR, CFR, and IMA.

Serum cotinine levels were measured with Calbiotech Cotinine Direct ELISA kit. The Calbiotech Cotinine kit is a solid phase competitive ELISA. The samples and cotinine enzyme conjugate were added to the wells coated with anti-cotinine antibody. Cotinine in the samples competes with a cotinine enzyme (horseradish peroxidase) conjugate for binding sites. Unbound cotinine and cotinine enzyme conjugate were washed off. Upon the addition of the substrate, the intensity of the color is inversely proportional to the concentration of cotinine in the samples. A standard curve was prepared relating color intensity to the concentration of the cotinine.

Statistical analysis

Results are expressed as mean and standard deviations. Statistical analysis was done using statistical software Stata 9.1 (College Statistix, Tallahassee, FL USA). The clinical characteristics between two data sets were compared using Chi-square test/Fisher exact test (categorical variables) and Student's *t*-test for independent samples/Wilcoxon rank-sum test for nonnormal data (continuous variables). The changes from baseline to follow-up were tested using Freidman *t*-test as the sample size was low. A $P < 0.05$ was considered as statistically significant.

Results

Seven male habitual tobacco chewers, with a mean age of 61 years (range 55–72 years), were included in the study. Conventional coronary risk factors seen in the study population are shown in Table 1. All patients had chronic stable angina along with a past history of anterior wall myocardial infarction in 2 patients and NSTEMI in 1 patient.

Majority of patients (5 out of 7) had angina New York Heart Association (NYHA III) and 2 had angina NYHA II. All were chronic tobacco chewers, with a history of tobacco chewing for more than 10 years. All patients were on aspirin, statins, beta-blockers, and nitrates. In addition, 4 of them were receiving clopidogrel, 5 were receiving angiotensin converting enzyme inhibitors, and 1 patient was receiving nicorandil prior to the procedure.

Coronary angiogram revealed significant left anterior descending artery (LAD) disease in all the included patients and additional mid right coronary artery (RCA) disease in 2 patients. The location of LAD lesions was proximal in 4 and mid in 3 patients. RCA disease was in the mid segment in both patients. RCA was studied in one of them for hemodynamic study as it was the last vessel to be stented.

All patients had high levels of baseline cotinine and follow-up levels at 15 and 30 min. Observed values were above accepted level of 5–100 ng/ml (Enzyme Immunoassay[EIA] values) and were very high in most of the patients as shown in Figures 1-4.

Table 1: Baseline characteristics

Variable	Value
Age (years)	61 years (55-72)
Male gender	7 (100)
Angina on exertion	
NYHA III	5 (70)
NYHA II	2 (28)
Conventional risk factors	
Hypertension	2 (28)
Diabetes mellitus	1 (14)
Dyslipidemia	4 (56)
Smoking	0 (0)
Past history of coronary artery disease	3 (42)
AW-STEMI	2 (28)
NSTEMI	1 (14)
Lipid profile	
LDL	112±18
HDL	39±6
VLDL	132±34
TG	25±7
Treatment received	
Aspirin	7 (100)
Clopidogrel	4 (56)
Statin	7 (100)
Beta-blockers	7 (100)
Nitrates	7 (100)
ACE inhibitors	5 (70)
Nicorandil	1 (14)
Duration of tobacco chewing in years	14 (10-20)
Coronary angiography profile	
DVD	3 (42)
SVD	4 (56)
LAD proximal	3 (42)
LAD mid	4 (56)
LAD total	7 (100)
RCA mid	2 (28)
RCA total	2 (28)
PCI performed with DES	7 (100)

Data expressed as *n* (%), mean±SD or median (minimum-maximum), wherever applicable. NYHA: New York Heart Association, AW: Anterior wall, STEMI: ST elevation myocardial infarction, NSTEMI: Non-ST elevation myocardial infarction, ACE: Angiotensin converting enzyme, SVD: Single vessel disease, DVD: Double vessel disease, LAD: Left anterior descending artery, RCA: Right coronary artery, LDL: Low density lipoprotein, HDL: High density lipoprotein, VLDL: Very low density lipoprotein, TG: Triglycerides, SD: Standard deviation, PCI: Percutaneous coronary intervention, DES: Drug-eluting stents

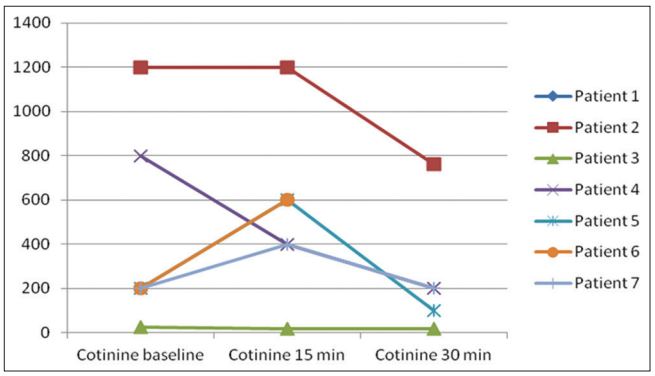

Figure 1: Serum cotinine concentration over 30 min.

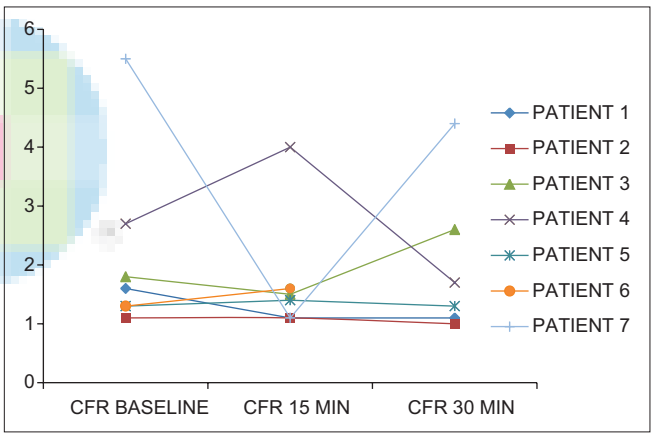

Figure 2: Graphic representation of changes in coronary flow reserve in seven individuals.

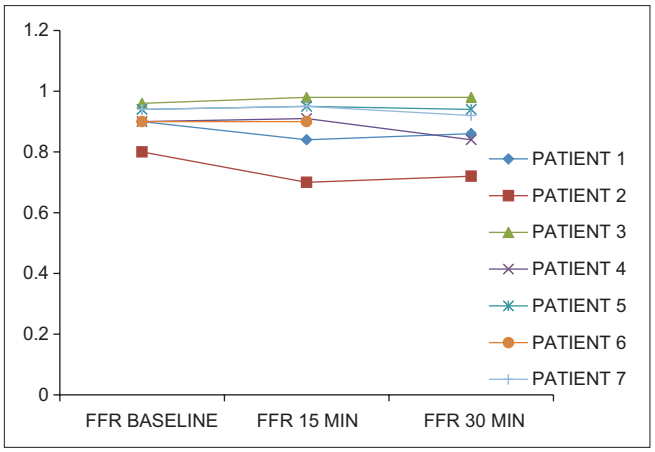

Figure 3: Graphic representation of changes in fractional flow reserve in seven individuals.

The various hemodynamic changes noticed during the study are detailed below. Baseline readings taken at 0 min (15 min after the completion of PCI) represent those values recorded before giving tobacco [Table 2].

Heart rate showed a mild increase toward the end of study at 30 min, which was not significant.

The systolic blood pressure (SBP) had shown a trend of increase at 15 min but again had a tendency to come toward normal at 30 min. Changes were statistically nonsignificant. Diastolic blood pressure (DBP) continued to show a rise which again was not significant. The patient no. 6 had bradycardia and hypotension at 15 min and reported bad taste prior to event probably because of vaso-vagal reaction due to the bitter taste of tobacco which had leaked out of breached tea-bag filter paper.

Majority of patients had low CFR even after achieving good PCI results which were evident by good FFR values post-PCI. This could be explained by high IMR values [Table 3].

Discussion

This is the first study of its kind, which has studied the microcirculatory hemodynamics in a relatively less well studied, but important public health hazard, that is, oral tobacco chewers. We found no major acute hemodynamic changes due to tobacco chewing in microcirculatory hemodynamics in habitual tobacco chewers despite an increase in cotinine levels.

All patients had very high levels of cotinine except 1 patient who had cotinine levels in acceptable cut off of 5–100 ng/ml. EIA results give values higher than high-performance liquid chromatography (HPLC) or chromatography (cut off 3 ng/ml) methods due to cross-reactivity with 3-OH-cotinine, a metabolite of cotinine. Cotinine has the standard range of 5–100 ng/ml as estimated by Calbiotech EIA method as opposed to < 5ng/ml by HPLC/chromatography techniques.[13,14] Cotinine metabolism is affected by factors such as race, gender, age, genetic variation in the liver enzyme CYP2A6, and/or by the presence of pregnancy, liver, or kidney disease. Given an average half-life of 16 h, cotinine levels reflect relatively short-term exposure to tobacco (i.e., over the past 3–4 days).[15] The serum cotinine levels for 1 patient could not be tested because of misplaced sample. Above observed high levels may be due to lower CYP2A6-mediated metabolism or lower hepatorenal clearance in the Indian population.

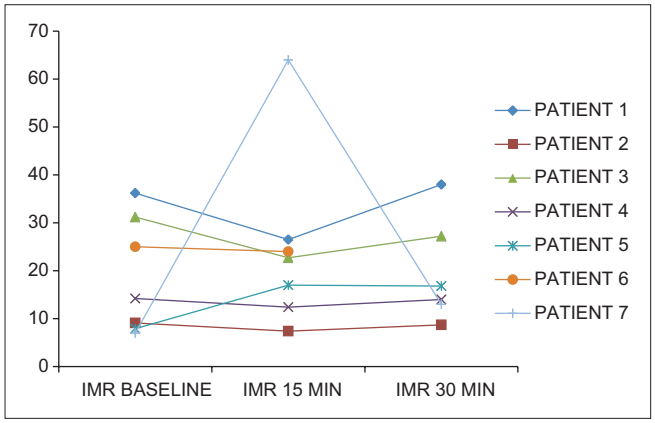

Figure 4: Graphic representation of changes in the index of microcirculatory resistance in seven individuals.

There was no procedural complication noted in any of the patient except one. Patient 6 had bradycardia and hypotension at 15 min reported bad taste prior to event probably because of vaso-vagal reaction due to the bitter taste of tobacco which had leaked out of breached tea-bag filter paper. However, the paradoxical response of nicotine toxicity cannot be ruled out.[16] Oral snuff tobacco increases heart rate, blood pressure, and epinephrine. Despite the increase in blood pressure, there is no decrease in either muscle sympathetic nerve activity or peripheral vascular resistance. Smokeless tobacco is a powerful autonomic and hemodynamic stimulus. Catecholamine (mainly epinephrine) release from the adrenal medulla likely contributes to this response.[17]

Comparing the baseline hemodynamic data, following trends were observed.

Heart rate showed a mild increase toward the end of study at 30 min which was not significant. This is in contrast to a previous study which had shown a significant increase over time but not seen in our group likely because of beta-blocker effect as all patients were on beta-blockers.[18] The SBP had shown a trend of increase at 15 min but again had a tendency to come toward normal at 30 min. DBP had a tendency for the rise as mentioned above. However, changes were statistically nonsignificant, and similarly, explained by the effect of beta-blockade. These observations are listed in Table 2.

IMR is a useful marker of microcirculatory resistance. Recently, a large multicenter registry including 253 patients in whom the IMR was measured immediately after primary PCI for STEMI found that patients with an IMR ≤ the mean value of

Table 2: Vital parameters

Parameter	0 min (*n*=7)	15 min (*n*=7)	30 min (*n*=6)	*P*
Heart rate	75.7 (±18.8)	74.5 (±17.5)	85.6 (±21.0)	0.85
SBP	131.2 (±16.4)	140.8 (±20.9)	136.6 (±20.4)	0.44
DBP	71.2 (±12.3)	76.8 (±9.2)	85.3 (±17.3)	0.09

All values mean and SD in parenthesis, *n* for number of patients. SD: Standard deviation, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Table 3: Coronary hemodynamic parameters following chewing of tobacco

Parameter	0 min (*n*=7)	15 min (*n*=7)	30 min (*n*=6)	*P*
CFR	1.6 (1.1-5.5)	1.4 (1.1-4.0)	1.5 (1.0-4.0)	0.46
FFR	0.90 (±0.05)	0.89 (±0.09)	0.87 (±0.92)	0.55
IMR	14.2 (7-36.2)	22.7 (7.4-64)	15.4 (8.7-38)	0.60

Data expressed as mean±SD or median (minimum-maximum), wherever applicable. *n* for number of patients. SD: Standard deviation, FFR: Fractional flow reserve, CFR: Coronary flow reserve, IMR: Index of microcirculatory resistance

40 had significantly lower rates of death or rehospitalization for congestive heart failure and death alone. It was also shown in multivariate analysis that the IMR was an independent predictor of both survival alone and survival or rehospitalization for congestive heart failure, whereas other common invasive methods for assessing microvasculature (CFR, thrombolysis in myocardial infarction [TIMI] myocardial perfusion grade, and TIMI frame count) were not.[19]

CFR was markedly reduced in the majority (5 out of 7 patients) and had a trend of further fall over time [Figure 2]. This has a major clinical relevance as despite optimal PCI results, that is, FFR more than 0.9 in most patients [Figure 3], CFR was still low. This can be explained that patients had both baseline and high IMR in 3 patients and 1 patient showing a steep rise in IMR at 15 min with recovery at 30 min [Figure 4]. These changes were in coherence with serum cotinine rise and fall, respectively.

Limitations

A very obvious limitation is the small sample size. Baseline high values before tobacco use are not very well explained. Furthermore, there was no reproduction of acute hemodynamic effects of tobacco chewing previously described. A control group of patients without habitual tobacco use could have help to confirm the baseline abnormalities in coronary microvascular hemodynamics.

To conclude, tobacco chewers have abnormal coronary microcirculation hemodynamics even following a successful PCI. Tobacco chewing leads to high serum cotinine concentration in the Indian patients. However, the coronary microcirculation and hemodynamics do not change acutely following tobacco chewing.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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