

# THE EFFECT OF NICOTINE GUM ON BLOOD PRESSURE AND HEART RATE

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## Abstract

**INTRODUCTION:** Smoking is an important risk factor of coronary artery disease. Nicotine replacement therapy (NRT) for smoking cessation should be considered, especially in coronary patients.

**METHODS:** Twenty-four healthy smokers, smoking an average of 20 cigarettes a day for 15 years and with moderate cigarette dependence (according to the Fagershtrum questionnaire score) were randomly assigned to 3 groups of 8 and followed up for 5 days. The first group consisted only of cigarette smokers. The smokers in the second group were given a piece of nicotine gum every two hours. The smokers in the third group were given a piece of non-nicotine gum (placebo) every 2 hours. The subjects' blood pressure and heart rate were checked 12 times during four daily intervals (between 7 AM and 12 PM, 1 PM and 6 PM, 7 PM and 12 PM, 1 AM and 6 AM) and recorded in related forms.

**RESULTS:** Systolic pressure was not significantly different in the three groups, but diastolic blood pressure of cigarette smokers was evidently higher than that of subjects who used nicotine and non-nicotine (placebo) gums.

**DISCUSSION:** Heart rate in smokers was higher than in nicotine and placebo users ( $P < 0.0001$ ). It seems that nicotine gum does not act as a cardiovascular disease risk factor. Hence in the context of smoking cessation efforts, its prescription to smokers with cardiovascular disease is recommended.

**Keywords** • Risk factor • NICO rest gum • Smoking • Systolic blood pressure • Diastolic blood pressure • Heart beat • CVD

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## Introduction

Today, nicotine replacements are widely used in the treatment of smoking dependence.<sup>1</sup> They are available in the form of gums, skin patches and nasal sprays.<sup>2</sup> The absorption rate of the released nicotine is the only difference between these products.

The nicotine released from nasal sprays is quickly absorbed into the mucus, increasing blood nicotine levels and reducing nicotine withdrawal symptoms following smoking cessation.<sup>3</sup>

Numerous studies have suggested that the use of nicotine replacements reduces cardiovascular accidents in smokers, hence their use has frequently been recommended.<sup>4,5</sup> Some studies, however, have referred to nicotine replacement therapy (NRT) in smokers with cardiovascular diseases as harmful.<sup>6</sup> A study conducted by Keeley and colleague demonstrated that the use of nicotine nasal spray did not increase the demand for oxygen in the myocardium.<sup>5</sup>

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The cigarette-related mechanisms which lead to cardiovascular accidents include:

1. Increased coagulability
2. Increased myocardial workload
3. Increased carbon monoxide (CO) levels and reduced hemoglobin oxygen transfer capacity
4. Impaired endothelial performance and structure
5. Constriction of coronary vessels
6. Catecholamine release<sup>6</sup>

Other toxins in cigarette smoke can also cause cardiovascular toxicity.<sup>7</sup> Cigarettes, nasal nicotine sprays and nicotine gums supply alternating doses of nicotine. By contrast, nicotine patches provide a steady supply of nicotine to the blood stream, maintaining it at constant levels.<sup>8</sup>

The increase in blood pressure and heart rate due to nicotine is mediated by activation of the sympathetic nervous system and the subsequent release of epinephrine and norepinephrine.<sup>9</sup>

Cigarette smoking contributes to wakefulness and sympathetic nervous system activity for 24 hours.<sup>10</sup> Cardiovascular accidents in patients with underlying coronary diseases are attributed to circadian variations of the sympathetic nervous system; these accidents most often occur between 6 AM and 10 AM,<sup>11,12</sup> when blood pressure increases following awakening, increased physical activity and release of catecholamines.

Some studies have implicated circadian blood pressure variations as the most important underlying cause of myocardial ischemia and possibly acute cardiovascular accidents.<sup>13,14</sup>

Thus, drugs or substances that can influence the pattern of blood pressure and heart rate variations and stimulate the sympathetic nervous system can increase the risk of cardiovascular diseases and be considered as a risk factor. To gain better insight into nicotine pharmacology and to evaluate the safety of various forms of nicotine including nicotine gums, we compared the pattern of changes in blood pressure and heart rate of cigarette smokers following smoking, use of nicotine gums, and placebo. Given the high price and inaccessibility of nicotine patches and sprays in Iran, we only used nicotine gums as nicotine replacement.

### Materials and methods

The subjects consisted of 24 men above 20 years with a mean age of 34 years who smoked an average of 20 cigarettes daily (15-40 cigarettes) and had a mean smoking history of 15 years (5-25 years). They were

selected among the participants in the 2004 Quit and Win Contest organized by Isfahan Cardiovascular Research Center, concurrently with 100 world countries. The subjects did not receive any medications.

To compare the cardiovascular effects of cigarette smoking and nicotine gums, the subjects were randomly divided into three groups, namely cigarette smokers, nicotine gum users, and placebo gum users.

*Cigarette smokers* smoked 16 cigarettes daily at regular intervals.

*Nicotine gum users* were given 16 pieces of nicotine gums to use daily at regular intervals.

*Placebo users* were given 16 pieces of placebo gum to use daily at regular intervals.

Given the pharmacokinetic properties of nicotine and its metabolites, the three groups were monitored for five days at the start of the study to achieve steady serum levels of the drug.<sup>14</sup>

The subjects' blood pressure and heart rate were checked 12 times during four daily intervals (between 7 AM and 12 PM, 1 PM and 6 PM, 7 PM and 12 PM, 1 AM and 6 AM) and recorded in related forms. Mean blood pressure during each interval was calculated and recorded. A member of the patient's family was trained during two 2-hour sessions to measure blood pressure using a mercury sphygmomanometer according to the WHO protocol.<sup>19</sup> Nicotine gums of the *Nicorest* brand available in Iran and placebo gums of the same shape and size were used. The smokers used cigarettes of the *Babman* brand. Student's t-test was used to compare mean blood pressure and heart rate between the two groups. ANOVA was used for comparisons between multiple groups.

### Results

Mean 24-hour blood pressure and heart rate was evaluated in the three groups. The results are presented in Table 1.

No significant difference was found between mean 24-hour systolic blood pressure and mean blood pressure in the three groups. However, mean diurnal blood pressure in cigarette smokers was markedly higher than in nicotine and placebo users.

Mean 24-hour diastolic blood pressure in smokers was notably higher than in nicotine gum and placebo users, with no significant difference between nicotine gum and placebo users. Mean 24-hour heart rate in smokers was notably and significantly higher than in nicotine gum and placebo users.

**TABLE 1.** Comparison of the effects of nicotine gums, cigarettes, and placebo on systolic and diastolic blood pressure

Blood pressure and heart rate	Systolic blood pressure (mmHg)			Diastolic blood pressure (mmHg)			Heart rate (beats per minute)		
	Placebo	Nicotine gum	Cigarette smoking	Placebo	Nicotine gum	Cigarette smoking	Placebo	Nicotine gum	Cigarette smoking
Mean 24-hour blood pressure (3 days)	113±10	114±10	115±11	62±6	62±6	65±6	62±7	62±6	68±9
Mean diurnal blood pressure	116±9	120±11	122±12	64±6	65±6	66±6	64±8	65±6	71±9
Mean nocturnal blood pressure	107±13	103±10	105±8	59±7	57±7	60±6	57±7	57±7	60±10
Mean diurnal and nocturnal blood pressure (7AM-7PM)	10±6	18±6	16±8	5±3	9±5	7±3	7±3	9±4	11±4

Mean heart rate in nicotine gum users was slightly but insignificantly higher than in placebo users.

### Discussion

This study was conducted to compare the effects of cigarette smoking and the use of nicotine gums on blood pressure and heart rate. The results of this study were in agreement with others, showing an increase in heart rate with smoking.<sup>14</sup>

The increase in heart rate seen with smoking was more evident than with nicotine gum or placebo use; this difference was more marked during daytime. Meanwhile, no significant difference was seen between heart rate in nicotine gum and placebo users; this may be explained by 8 hours of sleep-time nonsmoking (12 PM - 7 AM).

No statistically significant difference was observed between heart rate in nicotine gum and placebo users; this may be accounted for by the difference in serum nicotine levels following smoking and nicotine gum use. Other studies too, have highlighted the pharmacokinetic differences between different forms of nicotine. Following consumption of the same amount of nicotine in different forms, the highest blood nicotine levels were seen with smoking, nicotine sprays, nicotine patches, and nicotine gums, respectively; nicotine sprays were found to have a more rapid effect and produce more steady blood levels of nicotine.<sup>15</sup> Blood nicotine levels were not measured in this study, hence no definite judgment can be made in this regard.

Moreover, given the presence in cigarette smoke of substances besides nicotine, it does not seem entirely rational to attribute heart rate variations seen with smoking only to nicotine. In addition, several studies have highlighted the development of tolerance to the

effects of nicotine, suggesting a dose-dependent response.<sup>16</sup> Other factors implicated in cardiovascular diseases such as release of catecholamines, as well as the increase in platelet activity, B-thromboglobulin and other markers of the sympathoadrenal system were not adjusted for in this study, hence more accurate assessments are required. Nonetheless, the increase in heart rate following smoking in daytime, and activation of the sympathetic nervous system with the start of daily activities are all in agreement with studies which suggest a higher incidence of cardiovascular accidents in the early hours of the day.<sup>17</sup> Studies have suggested that 30% of cardiovascular accidents are related to cigarette smoking,<sup>18</sup> hence we recommend that physicians seriously consider the use of NRT to facilitate smoking cessation, especially in cardiovascular patients. NRT almost doubles the odds of success in smoking cessation,<sup>19</sup> while causing no tangible change in heart rate; therefore its use for aiding smoking cessation in patients with cardiovascular diseases should be considered. NRT has even been strongly recommended for treatment of diabetics, asthmatics and pregnant women.<sup>20</sup>

Diastolic pressure rose slightly in smokers compared to nicotine gum and placebo users. No difference in systolic pressure and/or the circadian pattern of blood pressure variations was seen between smokers and the other two groups. This is in agreement with the results of other studies which have monitored the smokers' blood pressure levels using noninvasive ambulatory methods.<sup>21,25</sup>

Studies applying invasive blood pressure monitoring methods (e.g. intra-arterial catheters) have reported slight and transient increases in blood pressure during NRT.<sup>11</sup>

No difference of blood pressure was seen between nicotine gum and placebo users; this may be explained by the route of use and the blood nicotine levels resulting from the use of nicotine gums.

Circadian variations of blood pressure and increased diurnal blood pressure can be attributed to the more active state of the sympathetic nervous system in daytime.

More precise assessment of daily blood pressure variations using accurate invasive methods, such as catheters or Holter monitoring is recommended.

In this study, blood pressure measurements were conducted by a family member and more than two measurements between 12 PM and 7 AM were not possible. Measurement and observer errors are also likely.

Other problems concerned lack of information about the subjects' living conditions, dissimilarities in the amount of exposure to daily stressors despite comparisons with the placebo group, and functional differences between the sympathetic nervous systems of subjects in confronting environmental stimulants; thus, further studies are recommended.

The subjects of this study were selected among the participants of the Quit and Win contest; the willingness of these individuals to stop smoking may have caused some difference between them and other smokers, hence distorting study results.

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