Cardiovascular Effects of Nicotine Gum and Cigarettes Assessed by ECG and Echocardiography

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INTRODUCTION

Cigarette smoking is one of the most firmly established risk factors for coronary heart disease (Kannel 1981). This risk can be dramatically reduced by discontinuation of cigarette smoking (Doll and Peto 1976; Hammond and Garfinkle 1969; Kannel 1981). Unfortunately, smoking cessation programs have low long-term success rates (Evans and Lane 1980; Raw 1978; Schwartz 1979). Several investigators attribute the maintenance of smoking behavior to a dependence upon nicotine (Gritz 1980; Jarvik 1970; Russell 1980). Nicotine induced withdrawal symptoms and nicotine seeking may account for cessation difficulty and high relapse rates. Nicotine chewing gum was introduced as a means of treating the pharmacological dependence during cessation of smoking (Ferno et al. 1973). The 4 mg dose results in blood levels of nicotine similar to a cigarette although without the "bolus" effect (see Russell and Jarvis in this volume). The 2 mg dose results in even lower blood levels. The purpose of using nicotine gum is to prevent abrupt withdrawal from nicotine and consequent symptoms and craving while supplying a substitute oral activity. Several recent studies attest to its efficacy in the alleviation of withdrawal (Hughes et al. 1984; Schneider et al. 1984; West 1984). Enhanced success rates in smoking cessation have been demonstrated in a number of recent placebo-controlled trials (Fagerstrom 1982: Hjalmarson 1984; Jarvis et al. 1982; Killen et al. 1984; Schneider et al. 1983). Since its introduction in the United States in 1984, this preparation is now widely available by prescription for the treatment of smoking dependence.

The purpose of this study was to examine and compare the acute effects on the cardiovascular system of nicotine delivered by smoking cigarettes versus chewing nicotine gum. Low and high nicotine cigarettes (0.2 mg and 2 mg) and 2 mg and 4 mg nicotine gum formed the four treatment conditions with each subject serving as his own control for all conditions. Cardiovascular evaluation included blood pressure, heart rate, electrocardiographic monitoring, and N-mode echocardiography, performed before and at

intervals up to 90 minutes after nicotine was introduced in eith form to healthy male smokers. Psychological responses wer elicited to determine whether there were any subjective response to treatment.

MATERIALS AND METHODS

Subjects

Fourteen paid volunteers were obtained through advertisements i the UCLA school newspaper. Subjects selected were males wh smoked at least one pack a day for two years or more and who wer healthy and active. Exclusion criteria included any history o cardiac, respiratory, gastrointestinal, or peripheral vascula disease. Subjects were required to be free of medications. On th first day of the study, a brief medical history was taken and pertinent physical examination was performed on each subject by cardiologist. This was followed by obtaining a resting bloom pressure (BP) measurement, a 12-lead electrocardiogram (ECG), an an M-mode echocardiogram (ECHO). If these tests were all withi normal limits and the echocardiogram was easily obtainable and o good quality technically (i.e. the subject was echogenic), the subject was recruited for an additional four days of study. Si males, ages 23 to 32 (mean age 27.3 ± 3.6 years), formed the final study group. Subjects smoked an average of 26 ± 5 cigarettes pe day for an average of 8.8 ± 5.1 years. Results of the cardiovascular tests were available to subjects' physicians upo request.

Materials

High nicotine (2.0 mg) and low nicotine (0.2 mg) cigarettes were provided by the National Cancer Institute. Merrell Dow Pharmaceuticals of Indianapolis, Indiana, provided 2 mg and 4 mg nicotine gum which was manufactured by A.B. Leo in Sweden. The gum (Nicorette) contained nicotine bound to an ion exchange resin which permitted the controlled release of nicotine. The gum was buffered to allow for rapid absorption through the buccal mucosa. Chewed gum was sealed in plastic containers and returned to Merrell Dow Pharmaceuticals for determination of residual nicotine. The residual amount was then subtracted from the initial dose to estimate the nicotine dose delivered.

Measurements

Cardiovascular measurements were taken in the supine position. A sphygmomanometer was used to obtain the systolic and diastolic blood pressure (BP) from the right arm in mm mercury (Hg). The mean BP was calculated as the difference between the systolic and diastolic BP, divided by three, and added to the diastolic BP. Electrocardiograms were taken with a Hewlett-Packard electrocardiograph. Standard echocardiographic techniques were used to obtain M-mode echocardiograms. The following measurements from the echocardiogram were made in triplicate and averaged wing a mini-computer (ECHO COMP by Digisonics, Inc., Houston, Texas):

1) left ventricular end-diastolic dimension (LVEDD) in mm at the onset of the R wave of the simultaneously recorded electrocardiographic lead II; 2) left ventricular end-systolic dimension (LVESD) in mm; 3) left ventricular ejection time (LVET) in seconds from the duration of aortic valve systolic opening; and 4) heart rate. From these measurements the left ventricular fractional shortening percent (FS%=LVEDD-LVESD/LVEDD) and velocity of circumferential fiber shortening (VCF=FS%/LVET) were calculated.

Carbon monoxide levels were measured by having the subject hold his breath for 20 seconds and then exhale into a carbon monoxide (CO) collection bag. The CO level was measured in parts per million on an Ecolyzer. A baseline CO level was taken on the first day of the study before the subjects were asked to abstain from smoking after 12 am on the day of study. On the following four treatment days, CO levels were obtained prior to treatment after abstinence from cigarettes for at least 11 hours and at 10 and 90 minutes after the beginning of each treatment.

psychological measures were obtained to determine whether subjects experienced subjective state changes over time and across treatments. Four items were tested on a lo-point verbal scale. The four items were: Are your hands shaky? Is your heart beating faster? Do you feel more alert? and Do you feel lightheaded? This scale was used previously and found sensitive to subjective changes from pre- to post-smoking (Schneider 1978). On the 10-point scale 1 represented “not at all" and 10 represented “very much.” In order to reduce random error and give the subject an opportunity to respond as exactly as possible, the immediately preceding response was read to the subject just before he gave his cur rent response.

Protocol

After informed consent was obtained, potential subjects who were still smoking were individually screened at 11:00 AM on Mondays. Six subjects were recruited for an additional four days of study. Subjects underwent testing of the four conditions (2 mg and 4 mg nicotine gum and 0.2 mg and 2 mg nicotine cigarettes) from 11:00 AM to 1:00 PM on the next four days in a randomly assigned order. Subjects were asked to abstain from smoking after 12:00 AM on each test day but not prior to the initial Monday visit. In addition, they were to abstain from caffeine in any form after 9:00 AM on each treatment day. Smoking abstinence was verified by testing the exhaled carbon monoxide levels. The dose of nicotine in the gum or cigarette was unknown to the investigator at the time of testing and the echocardiograms and ECG’s were read by two observers without knowledge of subject identity or of test condition.

On each test day, baseline heart rate (HR), BP, ECG, and ECHO were performed with the subject supine in a hospital bed prior to smoking a test cigarette or chewing a gum. Following the baseline measurements, repeat RR, BP, ECG leads 1, aVF, and V5, and ECHO of

the left ventricle and aortic root were performed at 5, 10, 20, 30, 45, 60, and 90 minutes after the test condition was started. The test questions were repeated at 5, 30, 60, and 90 minutes after the beginning of a treatment and carbon monoxide measurement was made at 10 and 90 minutes.

Smoking and chewing procedures were strictly controlled as follows: The cigarette was lit and held by the subject, who was instructed to take one puff every 30 seconds, hold each puff in for 5 seconds, exhale, and relax for 25 seconds. The timing was monitored and 10 puffs were completed in 5 minutes. For the gum treatment the subject chewed hard for 5 seconds and then held the gum in the cheek (for absorption) for 25 seconds. This cycle was timed and repeated every 30 seconds for 30 minutes. This procedure maximized and controlled the nicotine release while minimizing side effects.

Design

The design of the study was a 2x2x8 factorial for HR, BP, and echocardiographic measures, The first factor was type of treatment (gum vs. cigarettes); the second factor was dose (high vs. low nicotine); and the third factor was the 8 time periods at which measurements were taken. Psychological testing results made up a 2x2x5 factorial and CO measurements a 2x2x3 factorial.

Statistics

Repeated measures analysis of variance (ANOVA) with trends were performed on the data using a BMDP Statistical Software Program. One-way analysis of variance was used to compare baseline values across treatments for each measure. F tests for repeated measures were used to compare differences between baseline and 5 minute values and baseline and 30 minute values for heart rate and mean BP. These analyses were pre-planned and based on data for peak blood levels of nicotine reported after cigarette smoking (5 minutes) and after gum chewing (30 minutes) (Russell et al. 1980). Level of significance was chosen as $p < 0.05$ unless otherwise stated.

RESULTS

Nicotine Content in Chewed Gum

The average amount of nicotine absorbed by the subjects from the 2 mg and 4 mg nicotine gum was 1.1 ± 0.2 mg and 2.7 ± 0.4 of nicotine, respectively. These were estimated from values obtained for nicotine remaining in chewed gum. Thus, the high dose nicotine gum appeared to supply at least twice as much nicotine as the low dose nicotine gum. Five of six subjects reported an aversive or burning taste with the 4 mg gum and two of six subjects reported a burning taste with the 2 mg gum. Additional side effects consisted of nausea and belching in two subjects, and soreness of the throat in two others.

Carbon Monoxide Levels

Baseline levels of CO obtained before the subjects were asked to abstain from smoking are listed in table 1. CO levels obtained immediately prior to each treatment and at 10 minutes and 90 minutes after the treatment began are also listed in table 1 with ANOVA statistics presented in table 2. A main effect of condition ($p=0.02$) was noted which can be attributed to the significant rise in CO at 10 minutes for the cigarettes compared to the gum. The condition x time interaction was significant at the $p<.005$ level. There was no significant main effect of dose or dose x treatment interaction.

Heart Rates

The baseline and post-treatment HR responses are listed in table 3 as means ± SD for each condition with ANOVA statistics listed in table 2. The means are plotted in figure 1. There were no

TABLE 1. Carbon Monoxide Levels (ppm)

Sub	1	2	3	4	5	6	X ± SD
Base	25.0	26.0	5.0	26.0	57.0	40.0	29.8±17.4
C1							
Pre	17.0	14.0	4.5	11.0	10.0	21.0	12.9±5.8
10'	*	*	7.5	22.0	19.0	33.0	20.4±10.5
90'	13.0	14.0	6.0	16.0	14.0	27.0	15.0±6.8
CH							
Pre	6.5	17.0	4.0	11.0	8.5	21.0	11.3±6.5
10'	*	25.0	10.0	20.0	19.5	30.0	20.9±7.4
90'	9.0	18.0	6:0	16.0	13.5	23.0	14.2±6.2
GL							
Pre	17.5	12.5	3.0	11.0	8.0	21.0	12.2±6.5
10'	*	14.5	4.0	12.0	9.0	20.0	11.9±6.0
90'	15.0	11.5	3.5	9.0	7.0	14.0	10.0±4.4
G H							
Pre	19.5	10.5	4.0	11.0	8.0	24.0	12.8±7.5
10'	*	12.0	5.0	16.0	9.0	25.0	13.4±7.6
90'	12.5	10.5	4.0	13.0	8.0	19.0	11.2±5.1

Base, CO levels on Day 1 of study prior to abstention; CL, cigarettes containing low (0.2 mg) nicotine; CH, cigarettes containing high (2 mg) nicotine; GL, gum containing low (2 mg) nicotine; GH, gum containing high (4 mg) nicotine; Pre, immediately prior to intervention after at least 11 hours abstention from cigarettes: ppm, parts per million: Sub, subject; *, 10 minute CO measurement had not been added to protocol at the time of study.

TABLE 2. Analysis of Variance Statistics (p values)

	CO	HR	SBP	DBP	MBP	LVEDD	LVESD	FS%	VCF
Cond	0.02	0.61	0.74	0.54	0.57	0.92	0.76	0.69	0.95
Dose	0.18	0.01	0.01	0.06	0.31	0.11	0.20	0.88	0.87
Time	0.005	0.001	0.001	0.0009	0.0001	0.08	0.0004	0.0008	0.09
Cond X Dose	0.12	0.67	0.71	0.26	0.30	0.78	0.87	0.54	0.16
Cond x Time	0.0005	0.003	0.001	0.10	0.01	0.37	0.11	0.46	0.99
Dose x Time	0.77	0.29	0.96	0.43	0.61	0.51	0.33	0.61	0.43
Cond x Dose x Time	0.70	0.16	0.57	0.53	0.85	0.91	0.50	0.24	0.11

Cond, condition of cigarette vs gum; dose, low vs high nicotine; CO, carbon monoxide; HR, heart rate; SBP, systolic blood pressure (BP); DBP, diastolic BP: MBP, mean BP; LVEDD, left ventricular (LV) end diastolic dimension; LVESD, LV end systolic dimension; FS%, fractional shortening; VCF, velocity of circumferential fiber shortening; n=6 for all measures except n=4 for CO.

significant differences among the baseline values. A main effect of time (p=0.001) was observed with an increase in heart rate from baseline for all conditions with a return to near baseline values by 90 minutes. The significant dose effect (p=0.01) indicated that the higher doses of nicotine regardless of condition had a greater effect on heart rate than the lower doses. This dose effect was not interactive with time or condition. A significant condition x time interaction (p=0.003) revealed different peaks in time dependent on treatment (i.e., cigarettes vs. gum). The peak HR for the 90-minute study period was recorded at 5 minutes after the intervention began for the 0.2 mg and 2 mg nicotine cigarettes with an increaseover baseline of 7% and 28%, respectively. The increase in HR noted with the 2 mg nicotine cigarettes was significant (p<0.001). There was an insignificant 6% increase in baseline HR with the 2 mg nicotine gum observed at 5, 20, and 60 minutes. The peak HR for the 4 mg nicotine gum recorded at 30 minutes post-treatment represented a 12% increase which was also not significant (p=0.18).

Electrocardiograms

No changes occurred in the QRS complexes, ST segments, or T waves in leads 1, avF, or V_5 at any time during the various interventions. In addition, no ectopy was detected.

TABLE 3. Cardiovascular Measures

	CL	CH	GL	GH	CL	CH	GL	GH
	Heart Rate				Mean BP			
Baseline	67±9	64±7	64±9	67±7	72±3	73±8	7l±7	73±7
5 min	72±9	82±10	68±lO	71±9	74±2	8O±8	7O±5	73±8
10 min	70±11	74±l0	65±ll	72±8	7l±6	75±4	71±5	74±8
20 min	7O±9	73±7	68±ll	75±6	68±7	73±8	70±4	73±5
30 min	66±ll	69±9	66±7	75±9	67±5	7l±6	7O±4	73±7
45 min	65±9	71±7	65±lO	72±7	67±5	69±7	72±2	73±6
60 min	62±10	70±11	68±11	69±8	67±6	7l±6	70±3	70±6
90 min	66±9	66±8	60±5	65±11	68±6	73±3	7l±3	73±5
	Systolic BP				Diastolic BP			
Baseline	101±7	103±10	103±10	106±8	57±3	58±8	56±7	57±8
5 min	103±9	112±7	lOl±7	lO1±12	60±3	64±7	55±5	59±7
10 min	lOO±12	l04±7	lO2±7	103±9	57±6	60±5	56±7	59±9
20 min	97±ll	lO2±lO	98±7	103±6	53±8	58±7	57±4	58±7
30 min	96±10	lOl±7	99±8	102±9	52±6	55±6	56±4	59±7
45 min	97±7	99±10	99±6	l01±10	53±6	55±7	58±2	58±7
60 min	96±l2	lOO±7	97±5	lO2±1O	52±5	57±6	57±3	54±8
90 min	97±ll	l00±9	99±9	104±11	53±6	60±2±57+4		58±7

CL, low (0.2 mg) nicotine cigarettes; CH, high (2 mg) nicotine cigarettes: GL, low (2 mg) nicotine gum; GH, high (4 mg) nicotine gum; heart rate in beats/min; BP in mm Hg; values are means ±SD.

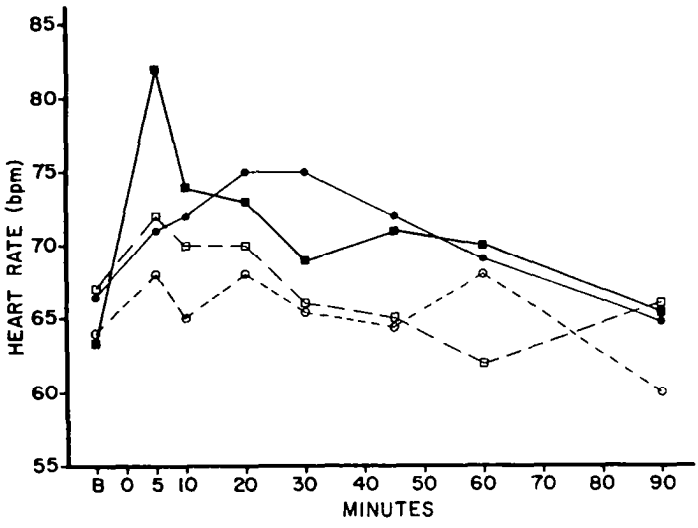

Figure 1. Mean heart rate in beats/min plotted versus time (minutes) for the four test treatments: □, low (0.2 mg) nicotine cigarettes; ■, high (2 mg) nicotine cigarettes; ○, low (2 mg) nicotine gum; ●, high (4 mg) nicotine gum. n=6. B, baseline.

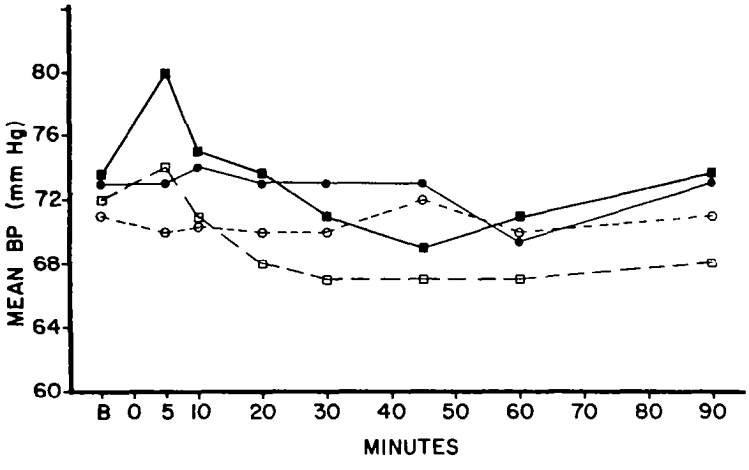

Figure 2. Mean blood pressure in mm Hg plotted versus time (minutes) for the four test treatments: □, low (0.2 mg) nicotine cigarettes: ■, high (2 mg) nicotine cigarettes: ○, low (2 mg) nicotine gum; ●, high (4 mg) nicotine gum. n=6. B, baseline.

Blood Pressure

The systolic, diastolic, and mean blood pressurevalues for the four conditions are listed in table 3. The mean BP is plotted in figure 2. No significant differences among baselinevalues for treatment conditions for systolic, diastolic, or mean BP's were noted. There was a significant condition x time interaction for systolic ($p=0.001$) and mean ($p=0.01$) BP. 'Ibis is attributed to an increase in both of these measures for cigarettes at 5 minutes in contrast to a decrease or no change in these measures after gum treatment (table 3). A peak rise in systolic BP of 2% and 9% and peak rise in diastolic BP of 4% and 12% were recorded at 5 minutes for the 0.2 mg and 2 mg nicotine cigarettes, respectively. The systolic BP did not rise above baseline for the 2 mg and 4 mg nicotine gum, and the diastolic BP rose less than 4% at anytime interval for both the 2 mg and 4 mg nicotine gum. The mean blood pressure rose a maximum of 3% and 10% for 0.2 mg and 2 mg nicotine cigarettes, respectively, at 5 minutes. The mean BP did not rise more than 1% above baseline at any time for the nicotine gum.

Echocardiographic Measures

The mean values for LVEDD and LVESD from ECHO are listed in table 4 in mm. No significant differences among baselines for the 2 variables were observed. A significant time effect for LVEDD of 0.08 and for LVESD of 0.0004 was present. However, there were no significant effects on LVEDD or LVFSD by dose or condition, and no significant interactions (table 2). The normal range for LVEDD in our laboratory is 38 - 57 mm and the normal LVESD is 21-39 mm. No value for the LVESD or LVEDD was out of the normal range during any part of the study.

The fractional shortening (FS) per cent is normally between 28% and 488. The values obtained in this study appear in table 4 and were all within the normal range. There was a significant ($p=0.0008$) main effect of time. The maximum change from baseline values was recorded over the first 10-20 minutes post-treatment and was a decrease of 3%, 3%, 11% and 9% for 0.2 mg and 2 mg nicotine cigarettes and 2 mg and 4 mg nicotine gum, respectively. By 90 minutes, FS% was within 3% of baseline values. There were no significant condition or dose effects or any significant interactions between or among condition, dose, and time (table 2).

Finally, the velocity of circumferential fiber shortening (VCF) was within the normal range of 0.89 - 1.60 at all times for all 4 conditions (table 4). No significant time, dose, or condition effects or any significant interactions were found (table 2).

Psychological testing

The only significant change ($p<0.05$) in subjective state reported for the 4 questions was for "Do you feel lightheaded?" . For this question there was a significant condition x time interaction ($p<O.004$) manifested by a significant increase in perceived lightheadedness at 5 minutes for the 2 mg nicotine cigarettes, only.

TABLE 4. Echocardiographic Measures

	CL	CH	GL	GH	CL	CH	GL	GH
	LVEDD				LVESD			
Baseline	50±2	50±l	49±2	51±5	33±2	33±l	32±l	33±2
5 min	49±2	51±4	49±2	50±4	33±2	34±3	32±l	33±2
10 min	50±2	51±3	49±2	51±5	34±3	34±2	34±2	34±2
20 min	50±2	51±3	48±2	52±5	33±2	34±3	32±2	34±2
30 min	49±1	51±3	49±2	52±5	32±2	34±2	33±2	34±3
45 min	49±3	51±3	49±2	5l±5	32±2	33±2	33±l	34±3
60 min	50±1	50±5	49±2	51±4	32±2	32±4	32±l	33±3
90 min	48±2	50±2	50±3	51±6	32±2	33±2	32±2	34±3
	FS				VCF			
Baseline			35±1	35±3	l.l5±0.06	1.09±O.10	1.13±O.11	1.12±0.03
5 min	33±3	34±2	34±3	34±3	1.07±0.13	1.13±0.10	1.07±O.09	1.14±0.11
10 min	33±4	33±2	31±3	33±3	l.O8±0.11	l.O4±0.08	l.O2±0.14	1.07±0.10
20 min	33±3	34±2	33±3	32±4	1.08±0.13	l.lO±0.12	1.10±0.10	1.05±0.13
30 min	35±3	33±3	33±3	34±3	1.14±O.12	1.03±0.11	1.05±O.09	l.O5±O.13
45 min	34±3	34±2	33±3	34±2	1.08±0.12	1.08±0.12	l.96±O.lO	1.12±0.14
60 min	35±3	37±2	34±3	35±1	1.06±0.14	1.15±0.12	l.ll±O.09	l.ll±0.06
90 min	34±2	33±2	34±4	34±3	l.lO±0.lO	1.07±0.10	1.08±0.10	1.06±0.16

CL, low (0.2 mg) nicotine cigarettes; CH, high (2 mg) nicotine cigarettes: GL, low (2 mg) nicotine gum; GH, high (4 mg) nicotine gum; LVEDD, left ventricular end diastolic dimension in mm; LVESD, left ventricular end systolic dimension in mm; FS, fractional shortening in %; values are means ±SD.

DISCUSSION

This study was designed to compare the cardiovascular effects of smoking a 0.2 mg or 2 mg nicotine cigarette with chewing a 2 mg or 4 mg nicotine gum and to begin to examine the safety of using nicotine gum as a method of smoking cessation.

The work of the heart, or oxygen demand, is dependent on four major factors: RR, preload, afterload, and contractility. RR can easily be directly measured. A significant increase in RR above baseline was noted only for the 2 mg nicotine cigarettes and consisted of a 28% increase from 64 ± 7 to 82 ± 10 beats/min noted at 5 minutes. Tachmes et al. (1978) reported heart rate and BP responses in eight healthy smoking subjects (five men and three women) before and after smoking low nicotine (0.3 mg) and high nicotine (2.0 mg) cigarettes. Their plotted mean values recorded at baseline and at 5 minutes after smoking agree almost precisely with our data, although S.D's were not reported. The increase in AR from baseline to 5 minutes for both low and high nicotine cigarettes was significant at $p<0.05$ in their study. The difference in sample size (n=8 vs. n=6) may account for the difference. Aronow et al. (1971) performed a similar study in male patients with a history of angina and found an increase in HR from 71.0 ± 11.0 to 86.8 ± 9.2 after smoking a high nicotine cigarette (2 mg) and an increase from 72.4 ± 11.1 to 81.0 ± 9.4 after smoking a low nicotine cigarette (0.3 mg). Both of these increases were significant.

The peak HR for the 4 mg nicotine gum was recorded as a 12% increase at 20 and 30 minutes, but this change was not significant. The timing of the peak HR correlates with previously reported peak plasma nicotine levels after chewing gum (McNabb et al. 1982; Russell et al. 1980). Wyberg et al. have reported a 15% increase in HR at 30 minutes after chewing nicotine gum containing 4 mg of nicotine for 30 minutes using a similar protocol (NYberg et al. 1982). This corresponded with peak whole blood nicotine levels which were also recorded by them at 30 minutes. Thus, a single dose of nicotine gum resulted in no significant change in HR in contrast to the significant increase observed with a single high nicotine cigarette over the 90 minutes studied. However, it is noteworthy that the peak HR achieved with 4 mg nicotine gum was greater than that observed with 0.2 mg nicotine cigarettes.

The mean BP, which is dependent on both the systolic and diastolic pressures, provides an indirect measure of afterload on the heart. The only significant changes ($p<0.05$) observed in the systolic, diastolic, and mean BPS were a 9%, 12%, and 10% increase from baseline noted at 5 minutes for the 2 mg nicotine cigarettes. The systolic and diastolic BPs recorded after gum chewing began were all less than the baseline, although not significantly less, indicating no effect of nicotine gum on BP. We did not observe the 7% increase at 30 minutes in systolic BP reported previously with 4 mg nicotine gum (Nyberg et al.). Their protocol differed from ours in that their subjects chewed the gum for 10 seconds instead of 5 seconds every 30 seconds. This may have been

responsible for the higher absorption of nicotine that they reported of 3.3 mg (range 2.9-4.0 mg) and may have resulted in the increase in systolic BP at 30 minutes.

The two remaining determinants of cardiac work are the preload (or stretch on the left ventricle) and contractility. The echocardiographically derived LVEDD provides a measure of preload, and FS% and VCF provide measures of contractility. None of these echocardiographic measures showed treatment effects. Thus, nicotine gum in a single dose given to healthy males with no known cardiovascular disease does not increase the work of the heart or adversely affect its function.

Raeder et al. (1979) assessed cardiac contractility using PEP, (pre-ejection period corrected for HR) and PEP/LVET in healthy male smokers and found no significant changes related to smoking low nicotine (0.1 mg) and high nicotine (2.6 mg) cigarettes. Our data is in agreement with this study but is in slight variance with a study by Rabinowitz et al. (1979) in 16 subjects (14 smokers). They reported an increase in LVEDD of 6% (cf. our 2% increase), in LVESD of 3% (cf. our 3% increase), and an increase in VCF of 13% from 1.12 ± 0.06 to 1.26 ± 0.09 (cf. our 4% increase) after smoking a high nicotine (2.5 mg) cigarette.

The experimental studies were performed after subjects had abstained from cigarettes for at least eleven hours. Mean baseline CO values for our six subjects were 29.8 ± 17.4 while smoking, and 12.4 ± 6.2 after abstaining for at least 11 hours. This average 58% reduction in CO levels is similar to data for 27 subjects previously studied with CO levels of 43.3 ± 15.3 while smoking and 16.4 ± 6.7 after abstinence for less than 1 day (unpublished data). This represented a 62% reduction in CO levels and was consistent with abstinence.

As expected, CO levels increased for both cigarette conditions immediately post-treatment, and such differences were not observed for the gum conditions. The results are similar to previously reported values (Aronow et al. 1971). No significant difference in the increase in CO levels at 10 minutes between the 0.2 mg and 2 mg nicotine cigarettes indicated that the differential increase in HR seen with the 0.2 mg vs. 2 mg nicotine cigarettes was likely due to the nicotine content and could not be ascribed to a variation in CO levels.

The only significant change in subjective state was an increase in lightheadedness reported at 5 minutes for the 2 mg nicotine cigarettes. The value for 0.2 mg nicotine cigarettes was increased at 5 minutes but not significantly. This subjective sensation may have been related to the increased CO and/or the rapid delivery of nicotine by cigarette smoking. It is unlikely that the increase in HR noted would be perceived as an increase in lightheadedness.

In summary, our study has shown no significant effect of 2 mg or 4 mg nicotine gum after a single dose on HR, BP, electrocardio-

graphic parameters, or echocardiographic measures of left ventricular function. This suggests that this modality may be a safe method from a cardiovascular perspective to use as an adjunct in smoking cessation therapy. We did not, however, examine the cardiovascular effects after multiple doses of gum as would be used clinically or give the gum to patients with significant cardiovascular or pulmonary disease. Both of these issues will require further study of nicotine gum.

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ACKNOWLEDGMENTS

The authors acknowledge the assistance of Stephanie Thessomboon in obtaining echocardiograms, Stacey Posner in administering the treatments, and Laura Read in data analysis. Alan B. Forsythe, Ph.D, provided statistical assistance in the analyses of the data This work was supported by a grant from Merrell Dow Pharmaceuticals.

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