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Ambulatory 24-h Blood Pressure Monitoring in Healthy, Middle-aged Smokeless Tobacco Users, Smokers, and Nontobacco Users

Gunilla Bolinder and Ulf de Faire

Ambulatory 24-h blood pressure monitoring was conducted in 135 healthy, normotensive, middle-aged (35 to 60 years) men, with no antihypertensive medication, to study the influence of habitual smokeless tobacco use (n = 47) and smoking (n = 29) on diurnal blood pressure and heart rate. Comparisons were made with nonusers of tobacco (n = 59). Adjustments were made for differences in age, body mass index, waist-hip ratio, physical fitness, and alcohol intake.

Daytime ambulatory heart rates were significantly ($P < .05$) elevated in both smokeless tobacco users and smokers compared with nonusers (69 ± 14 and 74 ± 13 beats/min, respectively, versus 63 ± 12 beats/min). In subjects ≥ 45 years old, ambulatory daytime diastolic blood pressures were significantly elevated, on average by 5 mm Hg, in both smokeless tobacco users and smokers ($P < .001$) compared with nonusers. Clinical measurements of heart rate and systolic blood pressure in smokers were significantly lower compared with the ambulatory mean values. Nighttime measurements showed only minor differences between the tobacco habit groups.

The higher heart rates and blood pressures noted during the daytime in smokers and smokeless tobacco users were most likely due to the effects of nicotine. A strong positive relationship was found between cotinine (major nicotine metabolite) and blood pressure in smokeless tobacco users (systolic blood pressure, $r = 0.48$, $P < .001$; diastolic blood pressure, $r = 0.41$, $P = .005$), whereas an inverse relationship was found in smokers (systolic blood pressure, $r = -0.12$, $P = .47$; diastolic blood pressure, $r = -0.03$, $P = .84$), indicating additional and more complex influences on vascular tone in smokers than the influence of nicotine in smokeless tobacco users. Am J Hypertens 1998; 11:1153–1163 © 1998 American Journal of Hypertension, Ltd.

KEY WORDS: **Ambulatory blood pressure, smoking, smokeless tobacco, nicotine.**

A large number of epidemiologic studies consistently show lower blood pressures in smokers compared with nonsmokers.[1] This finding is regarded as a paradox, because nicotine has potent sympatomimetic effects, affecting blood pressure levels and heart rate.[2–4] However, a few cross-sectional studies of smokeless tobacco users (one of which comprised >5000 smokeless tobacco users) suggested that smokeless tobacco users had higher blood pressures compared with both

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TABLE 1. CLASSIFICATION OF THE STUDY POPULATION INTO MAJOR TOBACCO HABIT GROUPS

	Nonusers (n = 59)	Smokeless Tobacco Users (n = 47)	Smokers (n = 29)	Years of Tobacco Use, Median (25th, 75th percentiles)
Never-users of tobacco	36			0
Exusers for ≥5 years*	14			12 (10–20)
Exusers for ≤5 years†	9			24 (19–29)
Smokeless tobacco users‡		27		25 (18–28)
Exsmokers, now smokeless tobacco§		20		24 (17–30)
Smokers‖			24	29 (20–30)
Smoking + smokeless tobacco use#			3	30 (23–35)
Former smokeless tobacco users, now smoking**			2	32 (30–35)

* *Stopped smoking or using smokeless tobacco >5 years prior to examination.*

† *Stopped smoking or using smokeless tobacco <5 years prior to examination.*

‡ *Current daily smokeless tobacco use for >6 months.*

§ *Stopped smoking >6 months ago, current daily smokeless tobacco users for >6 months.*

‖ *Current daily smoking for >6 months.*

Current daily smoking plus daily or occasional smokeless tobacco use.

** *Stopped using smokeless tobacco >6 months ago, current daily smokers for >6 months.*

smokers and nonusers.[5–9] Thus, there is a controversy as to whether the use of tobacco should be regarded as a risk factor for the development of established hypertension or not, although smoking is associated with a substantial increase in cardiovascular morbidity,[10] and hypertensive smokers multiply their cardiovascular risk compared to normotensive smokers.[11] Increased mortality from cardiovascular disease has been shown also in smokeless tobacco users compared with nonusers, although not to such a degree as in smokers.[12]

Ambulatory blood pressure monitoring in smokers and nonsmokers has been performed in a few studies, most of which indicate slightly higher blood pressure values in smokers, particularly during the daytime and in age groups >45 years.[13–16] However, in a study of normotensive Danish adults 20 to 79 years old, smokers exhibited slightly lower ambulatory blood pressure recordings compared with nonsmokers.[17] No ambulatory blood pressure monitoring of smokeless tobacco users has been performed up to now.

The use of oral smokeless tobacco results in blood levels of nicotine similar to those observed in cigarette smokers,[2,18] but smokeless tobacco users are not exposed to most other components of smoked tobacco. The more isolated exposure to nicotine in smokeless tobacco users makes it suitable to study blood pressure effects associated with long term nicotine exposure, and might help to elucidate the role of nicotine in the development of hypertension.

The aim of the present study was to use 24-h ambulatory blood pressure recordings to investigate whether the use of smokeless tobacco among healthy middle aged men, is associated with any alteration in blood pressure and heart rate during daytime and nighttime, compared with smokers and nonusers of tobacco, and to relate the findings of ambulatory blood pressure recordings to clinical blood pressure measurements.

METHODS

Subjects In 1993 there were 269 firefighters, 35 to 60 years old, in the Stockholm City Fire Brigade. In connection with the annual compulsory fitness test they were offered an extended health examination including 24-h ambulatory blood pressure monitoring. Of the 269 firefighters, 203 subjects (75%) were willing to participate, and 151 of these were called for investigation within the time limits of the study. Nonparticipating subjects (both nonresponders and those who were willing to come) were equally distributed amongst the nine different fire departments. All subjects were informed of the nature, purpose, and possible risks of the study prior to giving their voluntary consent to participate. The study protocol was approved by the ethics committee of Karolinska Hospital.

Subjects were divided into different tobacco habit groups as presented in Table 1. For intergroup comparisons nonusers, smokeless tobacco users, and smokers, defined according to the definitions in Table 1, were used. No subject was on antihypertensive medication. The recordings of 16 subjects were omitted because of inadequate technical quality (9 nonusers, 3 smokeless tobacco users, and 4 smokers), leaving 135 subjects for evaluation.

Physical Examination Body height and weight were measured and body mass index was determined (BMI in kilograms/square meter). Waist and hip circumferences were measured and the waist/hip ratio was calculated. Self-reported alcohol and coffee habits were registered as none, low, medium, or high consumption. Information on family history of hypertension was registered as answers to yes/no questions, as were questions about ongoing medication. Physical fitness was assessed by the maximal oxygen uptake as determined by a maximal exercise test, and dichotomized into ≥2.8 L/min or <2.8 L/min (the fire department limit for approving smoke-helmet equipment).

Blood Sampling Subjects were examined at 7:30 to 8:00 AM after overnight fasting and >8 h abstention from use of tobacco. Blood samples were drawn from an antecubital vein for the determination of nicotine and cotinine levels (the primary metabolite of nicotine). Cotinine levels were used to estimate the intake of nicotine. Cotinine, with a half life of about 18 h, is a good quantitative indicator of habitual nicotine intake.[19,20]

Casual Blood Pressure Measurement Blood pressure was determined, in the morning at 8:00 to 8:30 AM the day after the ambulatory monitoring was completed, by a standard mercury manometer with the cuff size adjusted to the circumference of the arm. Systolic (SBP) and diastolic (DBP) blood pressure was defined by the Korotkoff sounds phase I and V to the nearest 2 mm Hg after 5 min rest in a supine position, as the mean of two separate measurements. Heart rate (HR) was registered by palpation.

Ambulatory 24-h Blood Pressure Recording Ambulatory blood pressure was recorded using the Suntech Accutracker II (Suntech Medical Instruments Inc., Raleigh, NC). The method of measurement is auscultatory through a microphone over the brachial artery, using simultaneous electrocardiogram (ECG) recordings for R wave gating. Systolic and diastolic blood pressure was determined from phase I and V Korotkoff sounds. Blood pressure was recorded every 15 min during daytime (06:00 to 24:00) and every 30 min during the night (00:00 to 06:00), resulting in approximately 84 recordings per individual. Artifacts were defined as SBP > 250 mm Hg, DBP > SBP, DBP < 30 mm Hg, or DBP > 150 mm Hg. Data were analyzed as means of SBP, DBP, HR over 24 h, daytime, nighttime, and the averages of consecutive 3 h periods. Blood pressure variability was defined as the standard deviation of the mean value of the systolic or diastolic blood pressure during the time space referred to (24 h, daytime, nighttime, or 3-h periods) for each individual.

Diary The 24-h ambulatory recordings were all carried out during a weekday free from periods of normal firefighter duties or shiftwork, with daily activities recorded as periods of sleeping hours, unusual physical effort, smoking/smokeless tobacco use, alcohol intake, meals, and driving. The diary notations were principally used to register sleeping hours, and to identify exposure to unusual physical effort, like hard training or sport activities. Tobacco users were instructed to consume tobacco ad libitum according to their usual habits. Tobacco consumption data were analyzed only to confirm tobacco use during the registration period, because blood cotinine measurements before the ambulatory monitoring were used to estimate the habitual daily nicotine intake.

Statistics Means and standard deviations were calculated for all the anthropometric measurements and for blood pressure and heart rate recordings for the different time spaces, respectively. Intergroup comparisons were made for never-users of tobacco with smokeless tobacco users and smokers, using analysis of variance (ANOVA) and Fisher's PLSD (protected least significant difference) test for post hoc significance tests. Odds ratios (OR) and 95% confidence intervals were calculated for self-reported questionnaire answers in the three tobacco habit groups with the never-users as a reference group. Univariate linear regression was used to analyze the nature of relationships between blood pressure measurements, anthropometric data, and lifestyle factors. Covariates that might influence blood pressure were also entered in a multivariate regression model to adjust for their influence on the ambulatory blood pressure measurements.

RESULTS

Study Population Table 2 presents the basic characteristics of the study population. Waist-hip ratios were significantly higher in smokers, whereas no significant differences were found for age, body mass index, or sleeping hours in the three groups. In Table 3 the results of the questionnaire and physical exercise data are shown. Smokers consumed more alcohol and coffee and had significantly lower physical exercise capacity than both nonusers and smokeless tobacco users. Approximately one-third of the subjects exhibited a family history of hypertension in each of the three examined groups.

Blood Pressure Recordings There was a strong correlation between clinical and ambulatory recordings ($r = 0.69$ for SBP; $r = 0.47$ for DBP; $P < .001$). The results of the clinical measurements and the 24-h monitoring, after adjustments for differences in age, body mass index, waist-hip ratio, physical fitness, and alcohol consumption are shown in Table 4. Casual blood

TABLE 2. BASIC CHARACTERISTICS OF THE STUDY POPULATION

	Never-Users of Tobacco (n = 59)	Smokeless Tobacco Users (n = 47)	Smokers (n = 29)	P*
Anthropometric data				
Age (years)	45.1 ± 6.6	44.3 ± 6.4	47.2 ± 5.7	
BMI (kg/m^2)	25.7 ± 2.4	25.5 ± 2.2	25.0 ± 2.1	
Waist/hip ratio (cm/cm)	0.89 ± 0.05	0.89 ± 0.05	0.92 ± 0.06	<.001
Sleeping hours (n)	7.1 ± 0.8	7.0 ± 0.9	6.8 ± 0.9	
Tobacco use				
Number of cigarettes/day	0	0	18 ± 11	
Grams of smokeless tobacco/day	0	27 ± 15	0	
Plasma nicotine (μg/L)†	0.2 ± 0.3	4.5 ± 5.8	3.4 ± 2.7	
Plasma cotinine (μg/L)†	3.4 ± 2.7	359 ± 173	258 ± 161	

Values are means ± SD. n, number in each group. BMI, body mass index.

** Comparisons between smokers and never-users with analysis of variance (ANOVA), Fishers PLSD test for significance, significance level P < .05. No significant differences were found on comparing smokeless tobacco users with never-users.*

† After overnight abstension.

pressures were similar in nonusers and smokeless tobacco users and slightly, but not significantly, lower in smokers. During 24-h monitoring, smokeless tobacco users and smokers exhibited systolic blood pressures (in smokers also diastolic blood pressures) significantly higher compared with nonusers. This was most obvious during the daytime. The unadjusted mean values of the hourly recordings in the three tobacco habit groups are illustrated in Figure 1. If subjects ≥45 years old were considered, ie, 56% of the study population, there were significantly higher diastolic blood pressures (approximately 5 mmHg) found in both smokeless tobacco users and smokers, as compared with nonusers (Figure 2). Data on the 3-h mean values of systolic and diastolic measurements in subjects ≥45 years old, including ANOVA comparisons between the three tobacco habit groups are presented in Table 5. All daytime diastolic and most of the systolic blood pressure recordings in smokeless tobacco users were significantly elevated ($P < .05$) compared with nonusers. These differences were even more pronounced in smokers ($P < .001$) when compared with nonusers. Nighttime blood pressure recordings in subjects ≥45 years old did not, however, reveal any significant differences in the three tobacco habit groups, except for slightly elevated systolic blood pressures in smokers at the beginning of the night ($P = .04$) and for diastolic blood pressures in smokeless tobacco users at the end of the night ($P = .03$).

Blood Pressure Variability Comparisons of the blood pressure variability did not show any significant differences between the three tobacco habit groups, except for the nighttime systolic blood pressures in smokers ($P = .02$) compared with nonusers, as shown in Table 4. In Figure 3 the change in mean systolic and diastolic blood pressures from daytime to nighttime, expressed as a percentage, is shown. Both

TABLE 3. LIFE STYLE RELATED DATA ON THE STUDY POPULATION

	Never-Users of Tobacco (n = 59)	Smokeless Tobacco Users (n = 47)			Smokers (n = 29)		
	%	%	OR	CI	%	OR	CI
Coffee intake high*	19	21	1.2	0.5–3.0	31	2.0	1.7–5.4
Alcohol intake medium/high*	45	34	0.8	0.3–2.0	93	4.2	0.9–19
Physical capacity, low†	10	11	1.1	0.3–3.6	55	10.9	3.6–33
Family history of hypertension‡	34	26	0.7	0.3–1.6	38	1.2	0.5–3.0

** Alcohol and coffee intake dichotomized according to self-reported data: no or low intake = low; medium or high intake = high.*

† Assessed by maximal oxygen uptake < 2.8 L/min during exercise test.

‡ Self-reported known hypertension in either of the parents.

OR, odds ratio, comparisons made with never-users as reference group. CI, 95% confidence interval.

TABLE 4. BLOOD PRESSURE VALUES AT CLINICAL EXAMINATION AND THROUGH 24-h AMBULATORY MONITORING IN DIFFERENT TOBACCO HABIT GROUPS

Blood Pressure	Nonusers of Tobacco (n = 59)	Smokeless Tobacco Users (n = 47)	P*	Smokers (n = 29)	P*
SBP Casual†	124 ± 12	123 ± 13	ns	119 ± 18	ns
DBP Casual†	78 ± 7	78 ± 10	ns	78 ± 11	ns
Mean SBP, 24-h	123 ± 7	127 ± 9	<.05	128 ± 12	<.05
Mean DBP, 24-h	77 ± 9	79 ± 9	ns	81 ± 11	ns
Mean SBP, daytime	126 ± 8	131 ± 10	<.05	131 ± 12	<.05
Mean DBP, daytime	79 ± 9	81 ± 10	ns	83 ± 11	<.05
Mean SBP, nighttime	108 ± 8	106 ± 10	ns	110 ± 12	ns
Mean DBP, nighttime	66 ± 9	67 ± 10	ns	68 ± 12	ns
SBP Variability 24-h	13 ± 2	14 ± 3	ns	14 ± 3	ns
DBP Variability 24-h	11 ± 2	11 ± 3	ns	11 ± 2	ns
SBP Variability daytime	11 ± 2	11 ± 2	ns	12 ± 3	ns
DBP Variability daytime	10 ± 2	10 ± 2	ns	10 ± 2	ns
SBP Variability nighttime	9 ± 3	9 ± 3	ns	11 ± 3	<.05
DBP Variability nighttime	8 ± 2	8 ± 3	ns	9 ± 3	ns

All values are means and standard deviations adjusted for differences in age, body mass index, waist-hip ratio, physical training level, and alcohol consumption. Variability is calculated as the mean of the SD of each individual BP recording. n, number in each group; SBP, systolic blood pressure; DBP, diastolic blood pressure. Daytime, 06:00 to 24.00; Nighttime, 00.00 to 06:00; ns, not significant.

* *Comparisons between tobacco users and never-users, after adjustments, using Student t test. Significance level P < .05.*

† *Measured at 8:30 AM. after 5 min of supine rest.*

tobacco user groups showed greater change from day to night blood pressures compared with nonusers. Significant changes, however, were only recorded in diastolic blood pressures in smokeless tobacco users ($P = .01$).

Heart Rate Recordings Heart rate was significantly elevated in both smokeless tobacco users and smokers during day- and nighttime, compared with nonusers (69 ± 14 and 74 ± 13 beats/min, respectively, compared with 63 ± 12 beats/min). Mean values, adjusted for differences in age, body mass index, waist-hip ratio, physical fitness, and alcohol consumption are shown in Table 6. Compared to the clinical recordings after 5 min of rest, the mean heart rate during the 24-h ambulatory monitoring was on average 10% higher in nonusers and smokeless tobacco users and 20% higher in smokers. The unadjusted hourly mean heart rate values of the three tobacco habit groups are illustrated in Figure 4.

FIGURE 1. *Ambulatory blood pressure mean values (unadjusted) over 24 h in the three tobacco habit groups.*

Heart Rate Variability The mean heart rate variability was 11 ± 3 beats/min (10 ± 3 in the daytime and 6 ± 3 beats/min at night). Intergroup comparisons for the three tobacco habit groups exhibited a slightly greater variability in tobacco users (Table 6).

Physical Fitness, Heart Rate, and Blood Pressure The correlation between maximal oxygen uptake (liters/minute), as determined by a maximal exercise test, and 24-h heart rate demonstrated a highly significant correlation in the whole study group, showing a decreasing heart rate with increasing oxygen uptake ($r = -0.51$, $P < .001$). This finding was significant in all tobacco habit groups. There was a much weaker, but still significant, correlation between diastolic blood pressure but not systolic blood pressure and maximal oxygen uptake ($r = -0.21$, $P = .01$).

Confounding Factors Although there were no significant differences between the three tobacco habit groups regarding anthropometric measurements or age, there were still differences between the groups in physical fitness and other lifestyle related factors. When adjustments were made for all mean blood

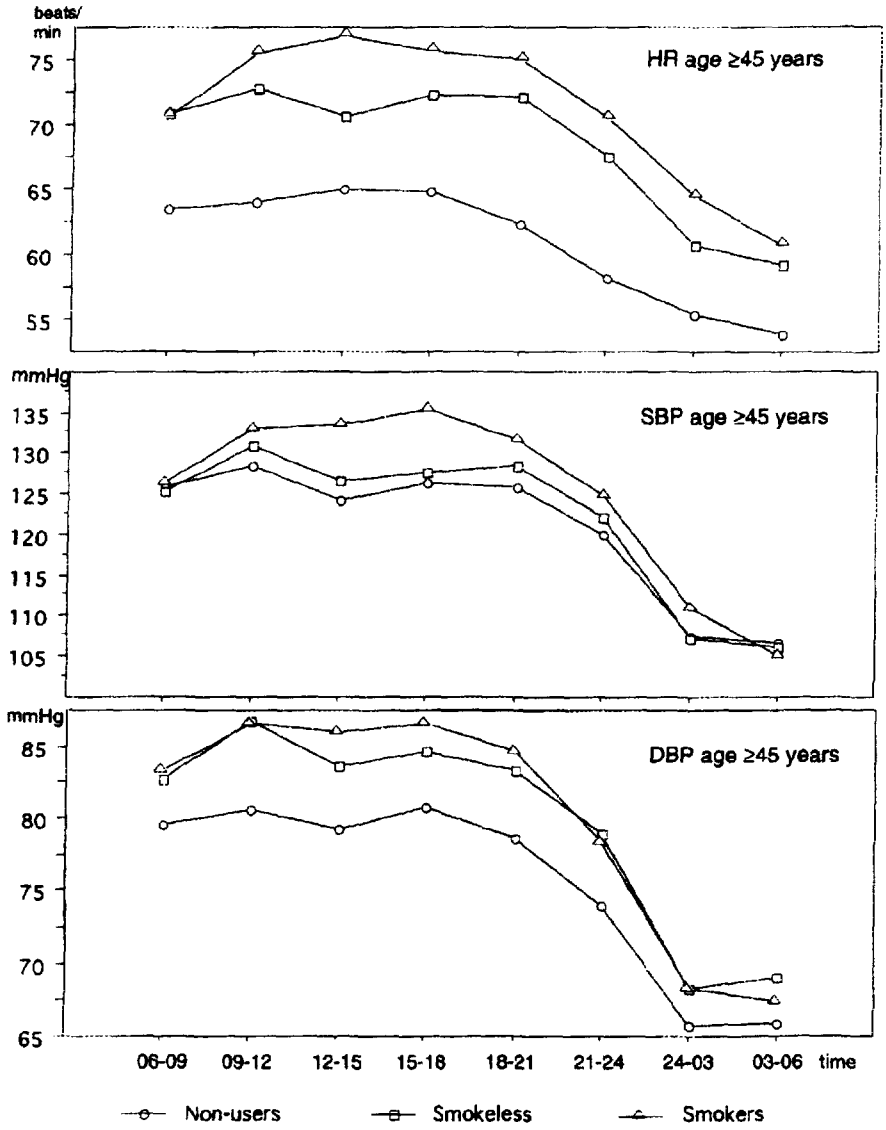

FIGURE 2. *Heart rate (HR) and systolic (SBP) and diastolic (DBP) blood pressure in subjects ≥45 years old (nonusers: n = 34; smokeless tobacco users: n = 23; smokers: n = 18). Mean values during 3-h periods of 24-h ambulatory blood pressure registration.*

pressure and heart rate values for the possible influences of age, body mass index, waist-hip ratio, physical fitness, and alcohol intake, by multivariate regression analysis, only physical fitness and body mass index had a significant influence on heart rate and blood pressure measurements. Adjusted values were generally slightly higher regarding blood pressure measurements and slightly lower regarding heart rate in the two tobacco user groups, but the differences remained essentially unchanged compared with nonusers.

Relationship Between Blood Pressure Measurements and Tobacco Consumption A linear regression analysis showed a highly significant correlation between blood cotinine values (the main metabolite of nicotine) and 24-h systolic and diastolic blood pressures of smokeless tobacco users (SBP, r = 0.48, $P < .001$; DBP, r = 0.41, $P = .005$), whereas smokers showed no such correlations (SBP, r = −0.12, $P = .47$; DBP, r = −0.03; $P = .84$), as shown in Figure 5. The relationship remained essentially unchanged even when controlling for differences in age and body mass index.

Relationship Between Family History of Hypertension and Ambulatory Blood Pressure In the whole study population, 32% had reported a family history of hypertension, and mean ambulatory systolic and diastolic blood pressures were significantly higher ($P < .05$) in these subjects: 126/81 mm Hg compared with 122/77 mm Hg in subjects without a family

TABLE 5. MEAN VALUES OF SYSTOLIC AND DIASTOLIC BLOOD PRESSURES IN SUBJECTS ≥45 YEARS OLD DURING 3-h PERIODS OF AMBULATORY BLOOD PRESSURE MONITORING, COMPARING TOBACCO USERS WITH NONUSERS OF TOBACCO

Hour		Nonusers of Tobacco (n = 34)	Smokeless Tobacco Users (n = 23)	P*	Smokers (n = 18)	P*
06:00 to 09:00	SBP	126 ± 14	125 ± 14	.59	126 ± 16	.73
	DBP	80 ± 12	83 ± 14	.003	83 ± 13	<.001
09:00 to 12:00	SBP	128 ± 14	131 ± 15	.03	133 ± 16	<.001
	DBP	81 ± 13	87 ± 15	<.001	87 ± 14	<.001
12:00 to 15:00	SBP	124 ± 15	134 ± 18	.08	134 ± 18	<.001
	DBP	79 ± 13	84 ± 17	<.001	86 ± 13	<.001
15:00 to 18:00	SBP	126 ± 14	128 ± 14	.34	135 ± 19	<.001
	DBP	81 ± 13	85 ± 14	<.001	87 ± 13	<.001
18:00 to 21:00	SBP	126 ± 13	129 ± 13	.02	132 ± 17	<.001
	DBP	79 ± 12	83 ± 13	<.001	85 ± 12	<.001
21:00 to 24:00	SBP	120 ± 12	122 ± 16	.1	125 ± 18	<.001
	DBP	74 ± 12	79 ± 16	<.001	78 ± 14	<.001
00:00 to 03:00	SBP	107 ± 11	107 ± 15	.91	110 ± 17	.04
	DBP	66 ± 11	68 ± 16	.09	68 ± 14	.09
03:00 to 06:00	SBP	107 ± 11	106 ± 12	.6	105 ± 15	.3
	DBP	66 ± 11	69 ± 12	.03	67 ± 14	.3

n, number in group; SBP, systolic blood pressure; DBP, diastolic blood pressure. All values are means and standard deviations.

ANOVA comparisons are made with nonusers as reference group.

** Fishers PLSD test for significance (P < .05 was considered significant).*

history of hypertension. In a linear regression analysis, the relationship of a family history of hypertension and ambulatory blood pressure values was strongest in smokers (r = 0.37, $P = .05$).

DISCUSSION

Comments on the Results Related to Tobacco Use

The main findings of the present study were the significant increase in heart rate in both smokeless tobacco users and smokers, indicating a persistent nicotine effect, together with the significant elevation of blood pressure in both smokers and smokeless tobacco users >45 years of age, which might be taken as a reason for long term tobacco use as a contributing factor in the development of sustained hypertension. Although the peak cardiovascular responses to nicotine have been shown to decline to normal values within 2 h after a given dose despite only small differences in nicotine levels, recurrent doses of nicotine always involve momentary stress effects on the cardiovascular system.[2,3] It should be noted that Swedish smokeless tobacco does not contain licorice, a substance which, some American studies suggest, contributes to blood pressure elevation.[7,21]

There are two paradoxes regarding vascular tone and the pharmacologic effects of nicotine: the constant finding of lower resting blood pressures in smokers together with a negative dose-response relationship with lower blood pressures observed as the number of cigarettes smoked increased[1,22–24]; and the lower prevalence of angina pectoris in smokers compared with nonsmokers.[25] Neither of these findings are compatible with the prominent increase in cardiovascular morbidity in smokers. As shown in the present study, the more isolated exposure to nicotine in smokeless tobacco users seems to involve significant effects on heart rate and blood pressure in healthy subjects. Smokers also exhibited a similar influence during 24-h monitoring, demonstrated also by other investigators.[13–16] There might, therefore, be a more complex influence involving other inhaled pharmacologically vasoactive substances when smoking, entailing a transient decline in blood pressure following cessation of smoking analogous to a type of withdrawal phenomenon.[1] A possible autonomic imbalance with increased vagal influence in resting positions, or endothelial dysfunction influenced by nitric oxide, carbon monoxide, or other combustion products in tobacco smoke might be responsible for these effects. Blunted postural responses in autonomic cardiac regulation in smokers have been demonstrated.[26] A finding in the present study, supporting a multipharmacologic influence of smoking is the lack of correlation between blood cotinine levels and blood pressure measurements in smokers, demonstrated also by others,[24] whereas smokeless tobacco users exhibited a strong relationship.

Nicotine values, as shown in Table 2, were rather

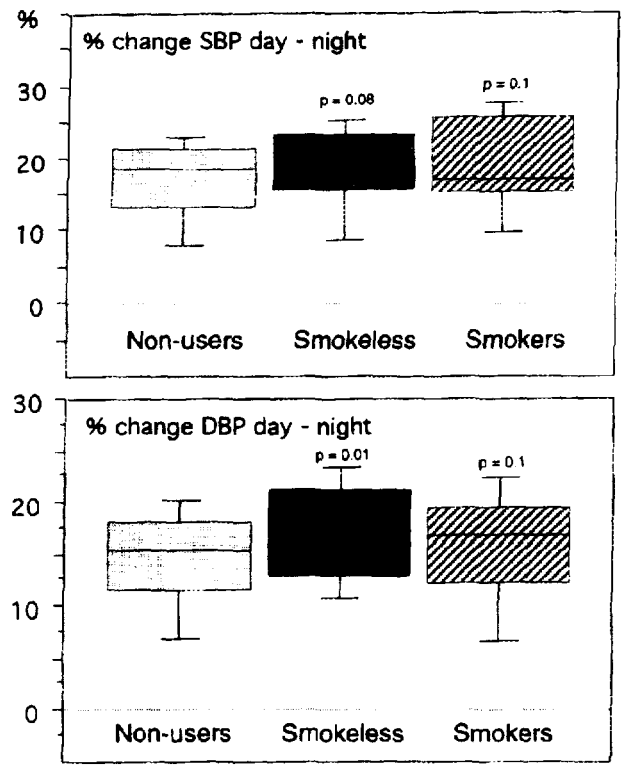

FIGURE 3. *Percent change from mean systolic (SBP) and diastolic (DBP) daytime blood pressures to mean nighttime blood pressures in the three tobacco habit groups. Box plots showing the 10th, 25th, 50th, 75th, and 90th percentiles. Comparisons with nonusers (ANOVA and Fisher's PLSD test) were significant P < .05) only for change in diastolic blood pressure in smokeless tobacco users.*

similar in smokeless tobacco users and smokers. The higher blood cotinine content in smokeless tobacco users is regarded as an indication of additional nicotine intake through the gastrointestinal mucosa by swallowing, and not reaching the central circulation until inactivated by first pass liver metabolism. It has been suggested that cotinine might have a relaxant effect on vascular smooth muscle,[13,24] and consequently smokeless tobacco users would most likely exhibit even lower blood pressures than smokers, according to their higher cotinine levels. This has not been demonstrated in any of the presented studies up to now.

Comments on the Results of the Whole Study Population All subjects in this study were normotensive and without medication. A metaanalysis of 23 studies of ambulatory blood pressure monitoring in >3000 healthy normotensive subjects[27] reported a mean daytime blood pressure of 123/76 mm Hg and a mean nighttime blood pressure of 106/64 mm Hg. Normotension was regarded as a blood pressure level lower than 140/90 mm Hg. In the present study the 24-h, daytime, and nighttime mean values were significantly higher compared with the results of the metaanalysis, but very similar to the findings of a study of a healthy population 20 to 70 years old in Sweden[28] (Table 7).

Family history of hypertension was found to be significantly correlated to higher ambulatory blood pressure values in this study, in accordance with previous studies.[29,30] The strong correlation of physical fitness, as determined by maximal oxygen uptake, and heart rate, found in all tobacco habit groups, are in accordance with previous studies.[31]

Comments on Methods The advantages of 24-h blood pressure monitoring include studying the diurnal variations in blood pressure levels resulting from the influence of lifestyle elements, such as mental stress, tobacco, coffee, alcohol, food, etc, and also

TABLE 6. HEART RATE VALUES AT CLINICAL EXAMINATION AND THROUGH 24-h AMBULATORY MONITORING IN THE DIFFERENT TOBACCO HABIT GROUPS

Heart Rate	Nonusers of Tobacco (n = 59)	Smokeless Tobacco Users (n = 47)	P*	Smokers (n = 29)	P*
Casual (beats/min)†	57 ± 9	60 ± 7	ns	58 ± 9	ns
Mean HR, 24-h (beats/min)	62 ± 12	65 ± 14	<.05	69 ± 14	<.05
Mean HR, daytime (beats/min)	63 ± 12	69 ± 14	<.05	74 ± 13	<.05
Mean HR, nighttime (beats/min)	54 ± 9	56 ± 12	<.05	58 ± 11	<.05
Variability, 24-h	9 ± 2	11 ± 3	<.05	11 ± 3	ns
Variability, daytime	9 ± 2	11 ± 3	ns	10 ± 2	ns
Variability, nighttime	6 ± 3	5 ± 3	ns	6 ± 3	ns

During the 24-h monitoring, on average 84 measurements/individual were performed. All values are means and standard deviations adjusted for differences in age, body mass index, waist-hip ratio, physical training level, and alcohol consumption. Variability is calculated as the mean of the SD of each individual heart rate recording.

* *Comparisons between tobacco users and never-users, after adjustments, using Student t test. Significance level P < .05.*

† *Measured at 8:30 AM, after 5 min of supine rest.*

Daytime, 06:00 to 24:00; Nighttime, 00:00 to 06:00; HR, heart rate; ns, not significant.

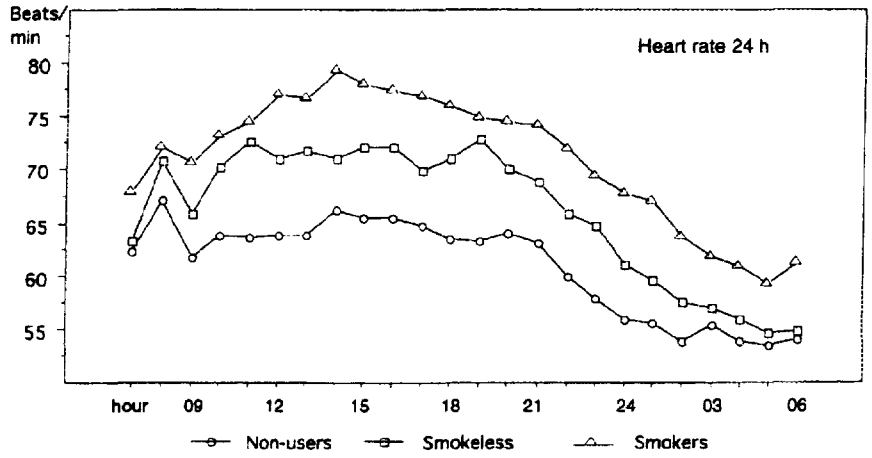

FIGURE 4. *Hourly mean values of heart rate during 24-h ambulatory blood pressure measurements, in the three tobacco habit groups. Smokeless tobacco users showed significant differences (P < .001) during all daytime measurements, but not at night, compared to nonusers. Smokers had significantly (P < .001) elevated heart rate compared to nonusers both by day and at night.*

studying pharmacologic treatment patterns.[16,32] However, ambulatory monitoring has limitations as conditions are less controlled than measurements taken at a clinic. Changes in physical activity during the period of monitoring account for about a third of the overall variance of blood pressure.[33] In the present study only ordinary daily activities without high physical demands were performed and there was no diary-reported difference in activity patterns between the three tobacco habit groups. Still, this study was performed on physically very well trained middle-aged men, and significant differences in physical performance were observed only comparing nonusers with cigarette smokers.[34] The findings of the present study might therefore underestimate the cardiovascular effects of smokeless tobacco, because all subjects were more physically fit than a random sample of the population.

The standardized choice of 00:00 to 06:00 as sleeping hours can, of course, give rise to questions of misclassification of awake and sleeping recordings. As there were no significant differences in sleeping hours between the three tobacco habit groups, and as 90% of all subjects reported being asleep during the nighttime registration period, there is reason to believe that any possible misclassifications should be equally distributed in the three tobacco habit groups.

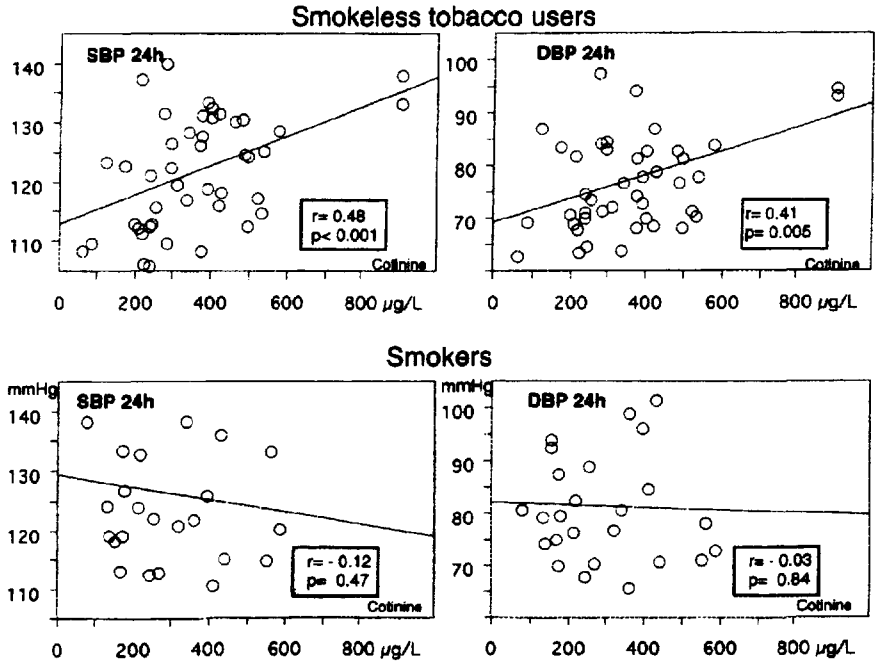

FIGURE 5. *Linear regression analysis of the relationship between mean 24-h ambulatory systolic (SBP) and diastolic (DBP) blood pressures and blood cotinine values in smokeless tobacco users (n = 47) and smokers (n = 29); P < .05 are regarded as statistically significant.*

TABLE 7. COMPARISONS OF THE RESULTS OF THE PRESENT INVESTIGATION WITH STUDIES ON NORMAL VALUES OF AMBULATORY 24-h BLOOD PRESSURE MONITORING IN MEN

	Stæssen et al[27] (n = 1683*)	Nyström et al[28] (n = 100*)	Present Study, 1997 (n = 135)
Age (years)	20–79	20–70	35–60
Blood pressure (BP)			
24-h BP (mm Hg)	118/72	124 ± 9/76 ± 6	124 ± 9/78 ± 10
Daytime BP (mm Hg)	123/76	129 ± 9/80 ± 7	126 ± 10/80 ± 10
Nighttime BP (mm Hg)	106/64	110 ± 10/64 ± 8	107 ± 10/66 ± 10

Values are means ± SD (when available). n, number in each group.

** Information on men is calculated from data presented in the paper.*

CONCLUSION

Mild but long-standing blood pressure elevation can cause structural changes to both heart and blood vessels, thus contributing to the development of sustained hypertension.[35] There is no doubt that smoking cessation has tremendous effects on cardiovascular morbidity.[36] However, to stop smoking by switching over to smokeless tobacco does not seem to avert all of the cardiovascular risks associated with smoking. The finding of increased blood pressure in smokers during 24-h registration is contradictory to most reports on clinical blood pressure measurements but supports the results of several[13–16] although not all,[17] studies of ambulatory blood pressure recordings in smokers. The findings of elevated ambulatory blood pressures in smokeless tobacco users supports the results of earlier investigations.[8] The use of smokeless tobacco is increasing continuously in both the US and Sweden. Thus, it is important to consider that a proportionately small increase in cardiovascular morbidity due to the habit has obvious effects at a public health level, because cardiovascular disease remains the leading cause of death in these countries.

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