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Short- and Long-Term Effects of Smoking on Arterial Wall Properties in Habitual Smokers

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Objectives. This study investigated the short-term effects of smoking on hemodynamic function and distensibility and compliance of large arteries in habitual smokers. In addition, the effect of smoking was not measured in nonsmokers, but vessel wall properties were compared between smokers and nonsmokers (basal state).

Background. Smoking is a well known risk factor for atherosclerosis. Loss of distensibility and compliance of large arteries may play a role in the onset of atherosclerosis.

Methods. The distensibility and compliance coefficients of the common carotid and brachial arteries were determined from the arterial wall displacement during systole and the end-diastolic diameter by using a vessel wall movement detector and from the pulse pressure as assessed in the upper arm. Cardiac function (cardiac output, stroke volume) was measured with Doppler echocardiography. Systemic vascular resistance was calculated as mean arterial pressure divided by cardiac output.

Results. In habitual smokers, smoking one cigarette caused a sharp increase in blood pressure (6%) and heart rate (14%). Cardiac index increased (16%), mainly because of the marked increase in heart rate. Stroke and systemic vascular resistance indexes did not change significantly. Smoking enhanced forearm blood flow after wrist occlusion (17%), but total forearm blood flow was unchanged, suggesting an increase in muscle blood flow and a decrease in skin flow. Because of higher blood pressure, the diameter of the elastic common carotid artery increased by 3% (passive phenomenon). Distensibility of the carotid artery decreased (7%), and as a result, carotid compliance was preserved. In contrast, despite higher blood pressure, the diameter of the muscular brachial artery did not change, suggesting an increased vascular tone. Brachial distensibility and compliance decreased (18% and 19%, respectively). Habitual smokers were comparable to nonsmokers with regard to blood pressure, cardiac function, vascular resistance and vessel wall properties of large arteries. Heart rate was higher in habitual smokers (14%).

Conclusions. These data indicate that in habitual smokers, smoking one cigarette causes short-term increases in arterial wall stiffness that might be harmful to the artery and increase the risk for plaque rupture. Except for a higher heart rate, no obvious long-term effect of smoking was observed on hemodynamic variables and arterial stiffness. Because acute cardiovascular events are mainly due to plaque rupture, the short-term effects of smoking might be a more important risk than long-term effects for these acute ischemic events.

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In western countries cigarette smoking is a major risk factor for cardiovascular mortality and morbidity independent of other risk factors, such as hypertension, hypercholesterolemia and diabetes mellitus (1). Hammond and Horn (2) have linked smoking to coronary artery disease and atherosclerosis. Since the time of these original observations the prevalence of smoking and mortality from coronary heart disease have declined, but 25% of all cardiovascular deaths in the developed countries are still attributable to cigarette smoking (3). Even in countries where the incidence of coronary heart disease is relatively low, smoking shows a relation to cardiovascular disease (4), and even passive smoking has been reported to increase the risk of death from ischemic heart disease and myocardial infarction (5). Epidemiologic studies have demonstrated a close association of smoking not only with coronary heart disease (3) but also with stroke (6), sudden death (1) and occlusive peripheral arterial disease (7). In addition, cigarette smoking seems to interact with hypertension, as indicated in the large hypertension trials in which one third of hypertensive men are smokers (8,9).

All studies have demonstrated a dose dependency of smoking and cardiovascular risk, but the risk appears not obviously related to the duration of the smoking habit (10). The Framingham Study has shown that for every 10 cigarettes/day, cardiovascular mortality in men is increased by 18% and in women by 31% (1). However, the effect of smoking on cardiovascular disease seems to be reversible. In the Framingham Study those who refrained from smoking had a 50% reduction in risk for coronary heart disease. The risk for cardiovascular death in smokers was comparable to that of nonsmokers within 1 year after cessation, although

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Table 1. Demographic Data for Smokers and Nonsmokers

	Smokers (n = 14)	Nonsmokers (n = 14)
Gender	9 M/5 F	9 M/5 F
Age (yr)	37 (25–55)	37 (25–54)
Weight (kg)	73 (55–88)	72 (52–93)
Height (cm)	175 (158–186)	174 (161–183)
BSA (m^2)	1.9 (1.6–2.1)	1.9 (1.6–2.0)

Values in parentheses are ranges. BSA = body surface area, calculated according to the formula of Du Bois and Du Bois (14).

for peripheral arterial disease the risk was not completely reversed (1). From the aforementioned studies, it can be concluded that cigarette smoking unfavorably affects the cardiovascular system by increasing the risk for atherosclerosis and cardiovascular events.

Increased arterial wall stiffness might play an important role in atherosclerotic disease and the occurrence of acute coronary events (11,12). Arterial distensibility and compliance are important determinants of the load on the arterial wall. These vessel wall properties can now be assessed noninvasively with a vessel wall movement detector system.

In the present study, the short-term effect of smoking on large arteries and other hemodynamic data was investigated in habitual smokers (study 1). In addition, these variables were compared with those in nonsmoking subjects (study 2).

Methods

Subjects. Fourteen healthy smokers participated in the study. They had been smoking an average of 23 cigarettes/day (range 13 to 60) for 17 years (range 5 to 30). The short-term effects of smoking (study 1) were studied in 12 of them. In addition, the smokers were compared with 14 healthy persons who had never smoked (study 2). The groups were matched for gender, age, weight, height and physical activity. Demographic data are shown in Table 1.

Study design. The subjects were not allowed to use caffeine-containing beverages or meals, and the smokers had to refrain from smoking for at least 4 h before examination. All hemodynamic measurements were performed after 15 to 20 min of supine rest in a quiet room (23 ± 1°C). Written informed consent was obtained from all subjects.

Study 1. Measurements were performed before and immediately after smoking one cigarette containing 1.3 mg of nicotine (Caballero filter). The cigarette was smoked under standardized conditions: Every 20 s, a puff of 5 s was taken, and the whole cigarette had to be smoked within 5 min. Vessel wall properties of the right elastic common carotid artery and the right muscular brachial artery were measured in separate sessions. Simultaneously, blood pressure and heart rate were recorded every minute. In addition, cardiac function and forearm blood flow were determined before and after smoking.

Study 2. With the same techniques used in study 1, vessel wall properties of the carotid and brachial arteries and cardiac function were assessed in smokers and nonsmokers. Blood pressure and heart rate were recorded every 2 min.

Measurements of hemodynamic function and vessel wall properties. Arm blood pressure and heart rate were measured with a semiautomated device (Dinamap, Critikon) on the left arm. Pulse pressure (ΔP) was defined as systolic minus diastolic blood pressure.

Vessel wall properties were measured in the recumbent position with a vessel wall movement detector system, as previously described by Hoeks et al. (13). Briefly, with this system, arterial diameter (D) and the distension during the cardiac cycle (ΔD) were measured for 5 to 6 s. The theoretic accuracy of the device is 3 μm for distension and 10 μm for arterial diameter. In our study, reproducibility of common carotid artery measurements was 4.5% (arterial diameter) and 7.9% (relative distension). For the muscular brachial artery, reproducibility of measurements was 13.4% and 2.5%, respectively. The means of three consecutive measurements were taken. Vessel wall properties were calculated as follows:

$$DC = (2\,\Delta D/D)/\Delta P, \quad [1]$$

$$CC = (\pi D \times \Delta D)/(2\,\Delta P), \quad [2]$$

where DC and CC are the distensibility and compliance coefficients, respectively. Cardiac output was examined in the left lateral position, using Doppler echocardiography (Ultramark V, ATL). Stroke volume was derived from the flow velocity-time integrals over the aortic valve. Heart rate was calculated from the RR interval, as derived from a simultaneously recorded electrocardiogram (ECG). The mean of six heartbeats was taken for each variable. Cardiac output was calculated as Stroke volume × Heart rate. Cardiac output and stroke volume were divided by body surface area to compute cardiac and stroke indexes (14). Systemic vascular resistance index was calculated as Mean arterial pressure/Cardiac index.

Forearm blood flow was determined by mercury strain gauge plethysmography, as described by Forconi et al. (15). An ECG-triggered strain gauge plethysmograph (Periflow, Janssen Scientific Instruments) was used. Subjects were in the supine position with the right arm at heart level. The whole arm was placed in an incubator to keep environmental temperature constant (28°C). In addition, the skin temperature of this arm was controlled by a skin electrode thermometer. In all subjects, skin temperature was similar before and after smoking (mean temperature 32.4°C). The mercury strain gauge was applied to the most voluminous part of the forearm. The cuff around the upper arm was inflated to 40 mm Hg to occlude the venous circulation. Under these conditions, volume changes, as detected by the mercury strain gauge, represent total (cutaneous and muscle) forearm blood flow. Hand circulation was eliminated by inflating a wrist cuff to suprasystolic pressure (220 mm Hg) for 4 min.

Table 2. Effect of One Cigarette on Hemodynamics Variables

	Before Smoking	After Smoking
Pressures (mm Hg)		
Systolic	112 ± 2	118 ± 3*
Diastolic	69 ± 1	73 ± 1*
Mean arterial	83 ± 2	88 ± 2*
Pulse	43 ± 2	45 ± 2
Heart rate (beats/min)	64 ± 3	73 ± 2*
Cardiac function		
Cardiac index (liters/min per m^2)	3.1 ± 0.1	3.6 ± 0.1†
Stroke index (ml/m^2)	48 ± 2	47 ± 2
SVRI (dynes·s·cm^{-5} per m^2)	1,751 ± 94	1,699 ± 81
Forearm blood flow		
Total forearm blood flow (ml/100 ml·min)	4.6 ± 0.7	4.5 ± 0.5
Flow after wrist occlusion (ml/100 ml·min)	2.7 ± 0.2	3.2 ± 0.2†

*$p < 0.001$, †$p < 0.04$. Values presented are mean value ± SEM. SVRI = systemic vascular resistance index.

After stabilization, a basal value was obtained without (5 min) and with (4 min) wrist occlusion. Only the last 3 min after wrist occlusion was used for evaluation.

Data analysis. The short-term effects of smoking in the smoking group (study 1) were analyzed with the nonparametric, matched paired signed-rank Wilcoxon test. Comparisons between smokers and nonsmokers in study 2 were made by the nonparametric Mann-Whitney *U* test. Results of both studies are presented as mean value ± SEM. A p value < 0.05 was considered statistically significant.

Results

Study 1. Results for blood pressure, cardiac function and plethysmography are presented in Table 2. After smoking, systolic and diastolic blood pressures increased significantly. Mean arterial pressure and heart rate were also elevated. Changes in pulse pressure were not statistically significant. Cardiac index increased after smoking, but stroke and systemic vascular resistance indexes were almost the same before and after smoking. Total forearm blood flow did not change after smoking. However, blood flow increased after wrist occlusion. Data for vessel wall properties are shown in Figure 1. After smoking, the arterial diameter of the common carotid artery increased slightly (before smoking 6.01 ± 0.17 mm, after smoking 6.17 ± 0.2 mm, $p < 0.05$), and carotid distensibility tended to decrease (before 30.6 ± 1.2 10^{-3}/kPa, after 28.5 ± 1.6 10^{-3}/kPa, $p = 0.06$). Arterial distension decreased significantly (before 518 ± 30, after 488 ± 28, $p < 0.05$). Compliance of the carotid artery was preserved after smoking (before 0.87 ± 0.05 mm^2/kPa, after 0.85 ± 0.06 mm^2/kPa). Brachial artery diameter did not change after smoking (before 3.65 ± 0.12 mm, after 3.67 ± 0.15 mm), whereas arterial distension decreased (before 229 ± 22, after 195 ± 18, $p < 0.01$). Distensibility (before 22.5 ± 2.3 10^{-3}/kPa, after 18.4 ± 2.0 10^{-3}/kPa, $p < 0.01$) and compliance (before 0.24 ± 0.03 mm^2/kPa, after 0.20 ± 0.02 mm^2/kPa, $p < 0.05$) decreased in the brachial artery.

Study 2. Table 3 shows the hemodynamic data in smokers and nonsmokers. Blood pressure (systolic, diastolic, mean and pulse pressures) and cardiac, stroke index and systemic vascular resistance indexes did not differ between smokers and nonsmokers. Vessel wall properties (diameter, distension, distensibility, compliance) of the elastic common carotid and muscular brachial arteries were also comparable between the two groups. However, heart rate was higher in smokers (71 ± 3 beats/min) than in nonsmokers (61 ± 3 beats/min, $p < 0.05$).

Discussion

Tobacco contains as many as 4,000 constituents. At present, nicotine is regarded as mainly responsible for the short-term hemodynamic effects of smoking. Nicotine has a

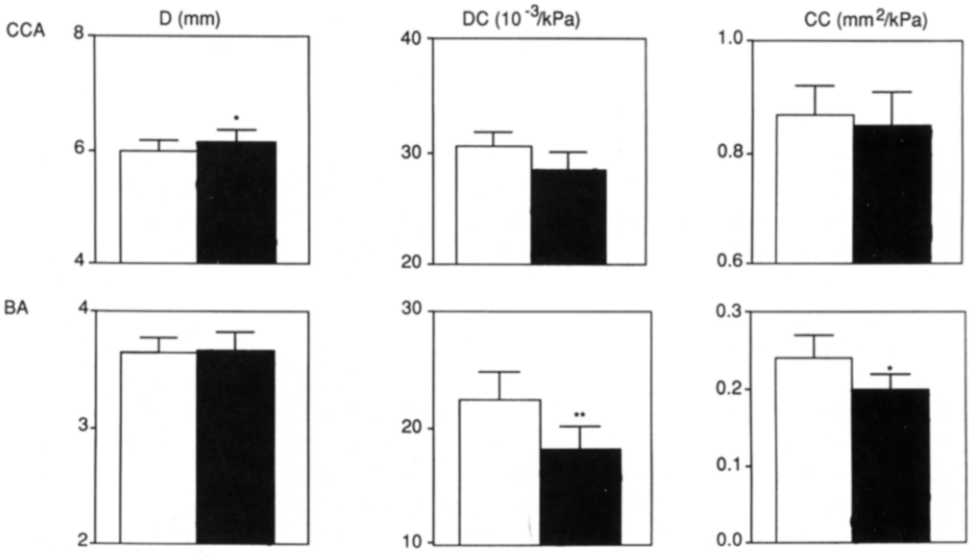

Figure 1. The short-term effect of smoking on vessel wall properties of large arteries before **(open bars)** and after **(solid bars)** smoking one cigarette. Data are mean value ± SEM. *$p < 0.05$, **$p < 0.01$ (difference between period before and after smoking). BA = brachial artery; CC = compliance coefficient; CCA = common carotid artery; D = diameter; DC = distensibility coefficient.

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Table 3. Hemodynamic Data for Smokers and Nonsmokers

	Smokers	Nonsmokers
Pressure (mm Hg)		
Systolic	117 ± 3	116 ± 3
Diastolic	71 ± 2	73 ± 1
Mean arterial	87 ± 2	87 ± 2
Pulse pressure	46 ± 2	43 ± 3
Heart rate (beats/min)	71 ± 3	61 ± 3*
Cardiac function		
Cardiac index (liters/min per m^2)	3.2 ± 0.1	3.0 ± 0.1
Stroke index (ml/m^2)	45 ± 1	51 ± 2
SVRI (dynes·s·cm^{-5} per m^2)	2,131 ± 95	2,346 ± 129
Vessel wall properties		
Carotid artery		
Diameter (mm)	6.05 ± 0.17	5.88 ± 0.1
Distension (μm)	488 ± 38	421 ± 32
DC (10^{-3}/kPa)	27.1 ± 2.2	25.8 ± 2.3
CC (mm^{-2}/kPa)	0.78 ± 0.07	0.69 ± 0.06
Brachial artery		
Diameter (mm)	3.56 ± 0.11	3.67 ± 0.13
Distension (μm)	202 ± 19	242 ± 26
DC (10^{-3}/kPa)	19.1 ± 1.8	23.5 ± 2.2
CC (mm^2/kPa)	0.19 ± 0.02	0.25 ± 0.03

*$p < 0.05$. Values presented are mean value ± SEM. CC = compliance coefficient; DC = distensibility coefficient; SVRI = systemic vascular resistance index.

biphasic effect. At low doses it causes ganglionic stimulation, with release of norepinephrine from nerve endings, release of epinephrine from the adrenal medulla and an enhanced neural discharge in the central nervous system. At high doses, ganglionic blockade, vagal stimulation or direct depression of the brain may result in opposite effects. The ultimate response is the net result of the stimulating and depressing effects of nicotine in each organ (16). In the present study, sham smoking experiments were not performed because previous studies in general could not demonstrate any effect of sham smoking (17,18). To achieve full regression of tolerance with nicotine (10), a 4-h nonsmoking period before examination was chosen. In general, heart rate increases 1 to 2 min after the start of smoking, and the effect lasts for 75 min (19), with a peak value after 5 to 10 min (20). Our examinations were performed after 5 min of smoking, which was at peak effect.

Long-term effect. In habitual smokers, smoking one cigarette caused a sharp increase in blood pressure (6%) and heart rate (14%). Cardiac index increased (16%), primarily due to a higher heart rate, whereas systemic vascular resistance was not altered. Forearm blood flow increased (17%) after wrist occlusion but remained unchanged without wrist occlusion. This observation suggests an increase in muscle blood flow and a reduced skin flow. Although published data are not always conclusive with regard to the effects of smoking, our findings are consistent with other studies (20–22). As in our study, in these studies the increment in blood pressure generally is lower than the increase in heart rate. Taken together, these short-term hemodynamic effects of smoking can be explained by the nicotine-induced sympathetic activation. Nicotine induces the release of both epinephrine and norepinephrine. Because efferent sympathetic nerve activity has been shown to be reduced in smoking (18), the increase in plasma catecholamines (23) instead reflects stimulation of the adrenal medulla or interaction with peripheral mechanisms (e.g., reduced norepinephrine clearance) (18). The net effect of smoking will be dependent on the mixed effects of epinephrine and norepinephrine at the different organ levels (24).

Short-term effect. Smoking one cigarette clearly influenced vessel wall properties of the elastic common carotid and muscular brachial arteries, although these vessels were affected differently. The arterial diameter of the carotid artery increased slightly (3%) after smoking. The vasodilation might be considered a passive phenomenon because in the same period arterial blood pressure was also higher. Distensibility of the carotid artery decreased after smoking (7%), and compliance of this artery was preserved because the decrease in distensibility was associated with an increased diastolic diameter (equation 2). In contrast, the diameter of the brachial artery did not change after smoking despite a higher blood pressure. This finding suggests an active mechanism, such as elevated vascular tone of this muscular artery. Elevated muscular tone could be due to an increase in plasma catecholamines. Because total forearm flow did not change, a flow-dependent effect is not likely. Distensibility of this artery decreased markedly (18%). Because of an unchanged diameter and decreased distensibility, arterial compliance of the brachial artery was significantly reduced under these circumstances (19%). The differences between the common carotid and brachial arteries may be due to a difference in the muscular content of the arterial wall in these arteries. In addition, it may be that with a larger diameter the carotid artery could distend less, resulting in decreased distensibility.

These findings indicate increased arterial wall stiffness after smoking. Other studies using indirect techniques, such as pulse wave velocity (19) and multigate pulsed Doppler echocardiography (17), also found transitory increases in stiffness of radial and femoral arteries after smoking, without changes in the arterial diameter of these muscular arteries (25).

After a 4-h nonsmoking period, heart rate at rest was higher in habitual smokers than in nonsmokers. This difference could not be explained by differences in physical activity level in the two groups because, on average, smokers and nonsmokers performed the same daily work and their sports activities were comparable. In previous studies, in long-term smokers (26) the heart rate has been persistently found to be elevated during abstinence, as a kind of withdrawal phenomenon. Blood pressure in the smokers in our study was not different from that in nonsmokers. Other studies have been inconsistent with regard to blood pressure in habitual smokers. Overall (26,27), casual as well as ambulatory blood pressure values in habitual smokers have

previously been found to be lower or similar to values in nonsmokers. In the present study, cardiac function was comparable in smokers and nonsmokers. Previous data on vascular resistance and cardiac function in long-term smokers are scanty, although long-term smoking has been associated with a reduced stroke volume (28). In the present smoking group, stroke volume was slightly reduced, but not significantly different from values in the control group. Vessel wall properties of the elastic and muscular large arteries were similar in habitual smokers and nonsmokers. Although no other published data are available for differences in vessel wall properties, particularly at the microcirculatory and arteriolar levels, functional and structural differences could not be demonstrated between smokers and nonsmokers (22,29). Thus, although the risk for cardiovascular disease is increased in habitual smokers (1,3), no effect on hemodynamic variables could be detected in this group of young habitual smokers in the present study.

Although smoking is related to atherosclerotic disease, little is known about the underlying mechanisms. Postmortem studies have shown that atherosclerotic lesions are more common in the aorta and the iliac, cerebral and coronary arteries of smokers than of nonsmokers, although findings in the latter vessels are inconsistent. In vivo, atherosclerotic disease was more extensively present in the carotid arteries of smokers than of nonsmokers (30). In addition, the effect seems to be age dependent because young smokers had far fewer lesions than older smokers (31). It cannot be excluded that changes in vessel wall properties could not yet be detected in the relatively young group of smokers in the present study.

Smoking may promote atherogenesis by different mechanisms, such as 1) higher blood pressure, 2) a direct toxic effect of nicotine on the endothelium (12), 3) increased permeability of the arterial wall and 4) reduced clearance properties of the wall (32). Other risk factors for atherosclerosis may also be involved in the hazardous effects of smoking, such as an unfavorably changed lipid profile (20,33), increased blood viscosity and alterations in platelet function and hemostasis (20,34,35).

In addition, according to the current view of atherosclerotic disease, plaque rupture is an important feature. It has been demonstrated that most of the acute coronary syndromes are due to the disruption of small, nonstenotic plaques (36). These small plaques are generally not detected with the present diagnostic techniques and might already be present in young smokers (36). Increased arterial wall stiffness, increased blood pressure and a higher heart rate are short-term effects of smoking that enhance the load on the vessel wall. In addition, at the site of atherosclerotic plaques, the distribution of circumferential and tensile stress is altered, which might further increase the load at the plaque (37). The smoking-induced increased load at the atherosclerotic plaque may induce plaque rupture and lead to acute ischemic events.

Conclusions. In habitual smokers, one cigarette induced hemodynamic changes compatible with a nicotine-induced sympathetic activation. In addition, smoking caused a short-term increase in arterial wall stiffness of both elastic and muscular arteries. Habitual smokers did not differ from nonsmokers in hemodynamic variables and properties of large arteries. Nevertheless, these young smokers might still be at risk for cardiovascular complications of atherosclerotic disease because each cigarette causes a short-term increase in the load on the arterial wall that might result in atherosclerotic plaque rupture and subsequent ischemic events.

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