Smokers have severely disturbed peripheral microcirculation

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Aim. **The aim of this study was to determine the effect of smoking a single cigarette on the blood flow rates in capillaries and arteriovenous anastomoses (AVAs) in light and heavy smokers in: a) the skin fold between the first and second fingers, and b) the pulp of the thumb.**

Methods. **Five light (10-12 cigarettes/day) and 5 heavy (>20 cigarettes/day) chronic smokers participated (4 men and 6 women, median age 40.5 years). The blood flow rates were measured by the ^{133}Xenon local washout method (capillaries, skin fold) and the heat washout method (AVAs, thumb pulp), respectively, before, during, and after smoking of a single Prince cigarette (0.9 mg nicotine).**

Results. **The blood flow rate (f) in mL(100 g(min)$^{-1}$ [standard error, SE] in skin capillaries of light smokers was 24.4 [9], 8.9 [1.8], and 10.4 [3.3] before, during, and after smoking of one cigarette; in heavy smokers, f was 23.6 [10.9], 16.1 [5.3], and 7.1 [2.9]; f in pulp AVAs of light smokers was 130.6 [14.9], 49.2 [24.8], and 119.7 [20.9] before, during, and after smoking; in heavy smokers, the corresponding results were 134.4 [19.1], 136.2 [13.5], and 143 [15.3]. Thus, the blood flow rate in capillaries of both light and heavy smokers was higher before smoking the test cigarette than previously observed in non-smokers. In light smokers blood flow rate in AVAs decreased during smoking with a factor of 2.6, and it returned to the pre-smoking level immediately after the end of smoking the cigarette. In heavy smokers, f remained unchanged before, during, and after smoking.**

Conclusion. **Smokers have severely disturbed peripheral microcirculation.**

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Key words: **Arteriovenous anastomosis - Microcirculation - Capillaries - Fingers - Perfusion - Smoking - Tobacco.**

There is evidence to suggest that smoking decreases the blood flow in the distal extremities through both the capillaries and the arteriovenous anastomoses (AVAs), and this response seems to be mostly pronounced for the AVAs.[1] A reduction of the blood flow during smoking has been observed in non-smokers as well as in habitual smokers, and the recovery phase after smoking seems to be slower in the latter group, (2 min vs 5 min) [2, 3] indicating that the microvascular responses to smoking could be chronic with the microcirculation being inured to smoke.[2] Apart from these local reactions, systemic increase in arterial blood pressure, heart rate, and plasma catecholamine levels have been observed during smoking, whereas finger temperature and finger skin blood flow decreased.[3, 4]

The distal blood flow is distributed between a nutritive component going through arterioles to capillaries and a predominantly thermoregulatory component passing through the AVAs. The reactions of these vessels in response to tobacco smoking have been studied by semiquantitative techniques such as laser Doppler fluxmetry in skin, videomicroscopy of venous limbs of capillaries, plethysmography, thermography, etc., but quantitative measurements are lacking. The ^{133}Xenon local washout method and the heat washout method [5] present 2 independent opportunities to measure the blood flow rate in absolute units selectively and atraumatically: for example mL(100 g · min)$^{-1}$, through each of the two microvascular beds, the capillaries and the AVAs, respectively.

Thus, we conducted the present study to determine the absolute blood flow rate (mL(100 g(min)$^{-1}$) under standardized conditions in light as well as in heavy smokers in a) the nutritive capillaries of the skin fold between the thumb and the forefinger, and b) in the AVAs of the thumb pulp; we also wished to determine the microvascular responses in terms of blood flow rate changes before, during, and after smoking of a single cigarette by these 2 groups of smokers.

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The increased capillary blood flow rate registered in smokers may be due to a degeneration of the elastic fibers in the wall of the arterioles of smokers so that arterioles distend to reduce peripheral resistance. Similar high blood flow rates have been observed in subcutaneous capillaries in patients operated for a ruptured infrarenal aortic aneurysm where a degeneration of elastic fibers in the arteriolar wall is a most likely explanation.[10] Other investigations have shown that the arteriolar response in skin was impaired in subjects who have smoked cigarettes for many years,[11] and that the recovery phase after smoking one cigarette is longer because the microcirculation is chronically inured in heavy smokers.[2] It still remains to be determined for how long time the capillary blood flow rate reduction remains after smoking of one cigarette.

The blood flow rate in AVAs before smoking was identical in light and heavy smokers, and baseline blood flow rate was around 10% higher in smokers than in non-smokers (130/134 mL(100 g·min)$^{-1}$ vs 120 mL(100 g·min)$^{-1}$ in non-smokers.[5] Blood flow rate in AVAs returned to pre-smoking values immediately after smoking was ended, whereas capillary blood flow rate kept on decreasing for at least 20 min.

The blood flow rate in the AVAs of heavy smokers did not change at all during smoking of one cigarette. In light smokers, blood flow rate in AVAs decreased with a factor of 2.6 during smoking. This corresponds well with the decreasing local finger temperature registered by Bornmyr *et al.*,[12] corresponding to a smoking induced closure of AVAs in the present study. Smoking of one cigarette took 5-6 min, and the third AVAs blood flow rate measurement was initiated immediately after smoking was finished, where blood flow rate was already normalized in most of the subjects. The results obtained in the heavy smokers may be caused by a long time influence of smoke preventing a normal cardiovascular response: the microcirculation becomes inured to smoke [2]. Heavy smokers may keep on chain-smoking trying to obtain a reaction on the cardiovascular system. Heavy smokers frequently report that they get dizzy when they are smoking their first cigarette in the morning. These findings correspond to the fact that after an overnight abstinence an increase of blood flow rate has been observed in the thalamus that is rich in nicotine receptors.[13] It is generally assumed that nicotine is responsible for the cardiovascular disturbances, but since tobacco smoke contains more than 5 000 individual substances there may be complex, yet unexplained, interaction.

In conclusion, smokers have severely disturbed microvascular regulation of the blood flow in the distal extremities.

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Materials and methods

We included 5 subjects smoking 10-12 cigarettes a day (light smokers) and another 5 subjects smoking at least 20 cigarettes a day (heavy smokers). None of the subjects smoked for at least 1 h prior to the study. All subjects were healthy volunteers, 4 men, and 6 women, median age 40.5 years (range: 31-53).

The protocol was approved by the local ethical committee, and all subjects gave their informed, written consent. Neither the participating subjects, nor the investigators had any financial interests in, or ties to, the tobacco industry, or affiliates, and funding was independent University allocations.

All measurements were performed under standard conditions with the subject in a sitting position, with a positive heat balance with warm hands and feet, in a room with a constant temperature of 22 °C, and smoking of one Prince cigarette containing 0.9 mg of nicotine was initiated.

^{133}Xenon washout (capillaries) was recorded continuously for 20 min in the skin fold between the thumb and the forefinger,[6] with the measurement starting 2 min before smoking.

The blood flow rate with the heat-washout method (AVAs) is made discontinuously,[5] so each measurement was repeated several times throughout: the first measurement was made before smoking; the second measurement was started immediately after the cigarette was lit; and a third measurement was made immediately after the cigarette was finished; further measurements were then taken until blood flow rate was back to the pre-smoking level.

All cigarettes were smoked down to the filter, and smoking of one cigarette took about 5-6 min.

The ^{133}Xenon washout method

A small diffusion chamber (diameter 1-2 cm) was created by a gas tight Mylar membrane (thickness 20 (μ) with double-sided adhesive tape at the edge.[6] This chamber was mounted on the skin fold between the right thumb and index finger. The skin fold is unique by consisting of only a cutaneous layer. A lead shield was covering the rest of the hand, so only the distal 2-3 mm of the skin fold was left free. About 0.1-0.2 mL of ^{133}Xenon gas dissolved in 0.9% NaCl was introduced into the chamber through a needle sewn through the edge of the adhesive tape at the edge of the Mylar membrane. After 3 min, the solution was aspirated through the needle, the chamber removed, the area wiped off, and surplus of ^{133}Xenon was blown away. The washout of ^{133}Xenon from the skin fold was recorded by a NaI(Tl) scintillation detector (adjusted around the 89 keV γ peak) coupled to a ratemeter and a printer; the washout was followed for 20 min with a sampling integration time of 10 s. The distance between the skin fold and the detector was kept constant (about 5 cm). The recorded count values were corrected for background activity and plotted against time in a semilogarithmic diagram. Subsequently, cutaneous blood flow rate was calculated using the Kety formula, $f=\kappa\cdot\lambda\cdot 100$, where k is the fractional washout rate constant of ^{133}Xenon, and λ is the partition coefficient (a table value) of 0.7 mL/g.

The heat-washout method

The probe is constructed with a thermostatically controlled cap, and it is capable of producing heat and measuring local temperature.[5, 7] The cap ensures isothermal temperature in the cap and in the probe. The probe was mounted on the pulp of the thumb and heated to 40 °C for a few minutes. After obtaining a stable heat gradient between the probe and the skin, the heating was turned off, and the local temperature under the probe was registered every 10 s until a stable baseline temperature was obtained. The baseline temperature was subtracted from the registered temperatures, and these differences, ΔT, were plotted in a semilogarithmic diagram against time. By using the principles of Kety as above, the absolute blood flow rates were calculated; in this context, λ is the fractional washout constant of heat =0.954 mL/g. To simplify, 1 mL/g was used.[5, 7]

Results

The results are shown in Table I and Figure 1. The blood flow rates measured in the thumb pulp, and in the skin fold before, during, and after smoking one cigarette were compared using Wilcoxon's signed rank sum test and the Mann-Whitney test for unpaired samples.

TABLE I.—*The blood flow rate in mL/100 g/min ± standard error of the mean (SE) a) in the cutaneous capillaries in the skin fold between the thumb and the forefinger by the ^{133}Xenon washout and b) in the arteriovenous anastomoses of the thumb finger pulp (AVA) measured by the heat-washout method; the measurements were made in 5 heavy smokers and in 5 light smokers before, during, and after smoking of a single cigarette.*

	Before smoking	During smoking	After smoking
Capillary			
Heavy smokers (n=5)	23.6±10.9	16.1±5.3	7.1±2.9
Light smokers (n=5)	24.4±9	8.9±1.8	10.4±3.3
AVA			
Heavy smokers (n=5)	134.4±19.1	136.2±13.5	143±15.3
Light smokers (n=5)	130.6±14.9	49.2±24.8	119.7±20.9

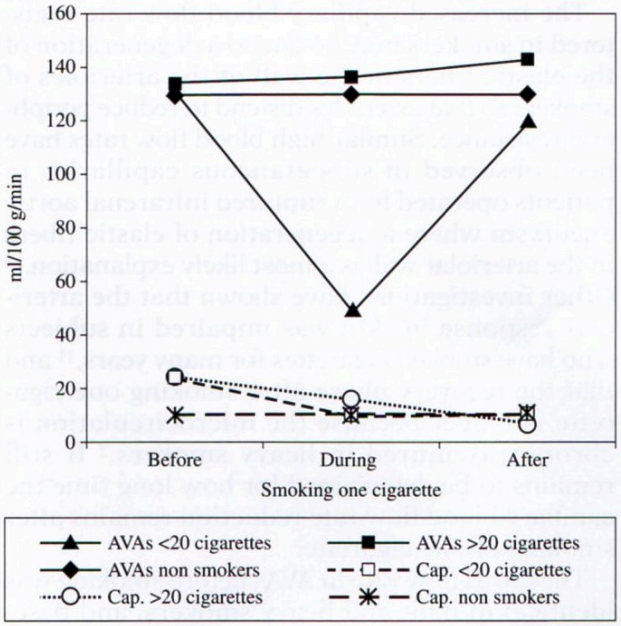

Figure 1.—The blood flow rate a) in the cutaneous capillaries (cap.) in the skin fold between the thumb and the forefinger by the ^{133}Xenon washout and b) in the arteriovenous anastomoses of the thumb finger pulp (AVAs) measured by the heat-washout method. The measurements were made in 5 heavy smokers and in 5 light smokers before, during, and after smoking of one cigarette. The results were compared to blood flow rates in non-smokers taken from our previous study.

Significant differences were observed in blood flow rate in AVAs in light smokers between results registered before and during smoking (P=0.01), and between results obtained during and after smoking (P=0.01). Significant difference was also obtained between heavy smokers and light smokers during smoking (P=0.01), and in all capillary measurements between and within these 2 groups, (P=0.01), except for the results measured before smoking compared to after smoking in light smokers.

Discussion and conclusions

The capillary blood flow rate in the skin fold between the first and second fingers in normal subjects as measured by the ^{133}Xenon washout technique under standardized conditions is around 10 mL (100 g(min)$^{-1}$.[8, 9] The present study showed that the capillary blood flow rate in skin is elevated 240% in both light and heavy smokers.

Washout of ^{133}Xenon from cutaneous tissue at normal skin temperature after a single gas labeling takes about 20 min (the duration of the observation period). The capillary blood flow rate was higher for both groups than our previously published values for non-smokers during the entire ^{133}Xenon washout period, but it decreased significantly throughout the measuring period in both groups of smokers (P=0.01). The first decrease was observed immediately after smoking was initiated. This result corresponds to that of Richardson [1] who found the maximal blood flow rate reduction within the first 2 min of the postsmoking period. The second decrease was observed about 7 min after the cigarette was finished. Blood flow rate then stayed low throughout the rest of the measuring period. Overall, the light smokers experienced a fall in capillary blood flow rate during smoking to 36% of the pre-smoking level; after smoking we only observed a marginal return to 42% of the pre-smoking level. In other words, smoking of one cigarette "normalized" the capillary blood flow rate in light smokers, since the measurements in light smokers during and after smoking of a cigarette yielded perfusion values similar to those of non smokers under standardized conditions.

The heavy smokers had a pre-smoking blood flow rate similar to that of light smokers; this is remarkable, since it appears that smoking in itself (and not the quantitative abuse) disturbs the microcirculation so that the basic capillary perfusion due to smoking increases to 2.4 times the value of non smokers.