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Effect of cigarette smoking on human precapillary sphincters

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Summary

1. Capillary filtration coefficient of human calf was measured by pressure plethysmography before and after cigarette smoking, which is known to release noradrenaline from nerve terminals of sympathetic vasoconstrictors. Calf blood flow and venous pressure–volume curves of the calf were also obtained before and after smoking.

2. Capillary filtration coefficient decreased by 19% when cigarette smoke was inhaled deeply at 30 s intervals for 12–15 min, indicating the closure of precapillary sphincters.

3. Calf blood flow decreased by 31% after smoking, indicating that arterioles were constricted. The degree of arteriolar constriction, however, was not strong enough to lessen the capillary hydrostatic pressure, since the absorption of tissue fluid into capillary blood vessels did not occur.

4. The venous system seemed little affected by cigarette smoking, since venous pressure–volume curves were unaltered.

Introduction

Inhalation of cigarette smoke is well known to cause arteriolar constriction in human limbs (Shepherd, 1963) by releasing noradrenaline from sympathetic vasoconstrictor nerve terminals (Burn, 1962). On the other hand, little attention has been paid to the possible effect of smoking on precapillary sphincters. If human precapillary sphincters are innervated by sympathetic vasoconstrictor nerves, as is the case in the cat and dog (Folkow & Mellander, 1960 ; Renkin & Rosell, 1962a, b; Cobbold, Folkow, Kjellmer & Mellander, 1963), then cigarette smoking may be supposed to induce the sphincter constriction. However, as previous studies showed that precapillary sphincters in human limbs are insensitive to sympathectomy (Kitchin, 1955) or sympathetic blockade (Rapaport, Saul, Hyman & Morton, 1952) suggesting lack of innervation, we cannot predict whether the actual constriction of sphincters occurs during smoking. The present experiments were undertaken to answer this question.

As a measure of the state of precapillary sphincter tonus, the capillary filtration coefficient (CFC) which is the product of the 'functional capillary surface area' and the filtration constant of capillary wall has been used (Cobbold *et al.*, 1963 ; Landis & Pappenheimer, 1964). Constriction of the precapillary sphincter, for

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example, lessens the capillary filtration coefficient by decreasing the number of functioning capillaries. Capillary filtration coefficient of human limbs can be determined by the pressure plethysmograph (Krogh, Landis & Turner, 1932; Landis & Gibbon, 1933) and this was used in the present study to observe the effect of smoking on precapillary sphincters.

Methods

The subjects were 4 healthy men. They smoked on average 5–10 cigarettes a day, but were asked not to smoke for 24 h before the experiment. They lay supine on a bed for at least 30 min before observations were begun.

A pressure plethysmograph applied to the human calf was used. The principal aim of this method was to measure small changes in the extravascular volume of the calf secondary to transcapillary fluid-movement. This was accomplished by collapsing blood vessels in the calf tissue at each measurement of volume. The apparatus (Fig. 1) was essentially the same as that described previously by Matsubara & Matsuda (1969). The right calf of the subject was covered by a loose sleeve of rubber and placed inside a double-walled lucite glass cylinder (16 cm inside diameter × 15 cm) of the plethysmograph. Both ends of the sleeve were everted and fixed to the ends of the cylinder. A rubber diaphragm and a metal plate, both of which had openings fitted to the subject's calf, were used to close each end of the cylinder. The plethysmograph was then filled with water, the temperature of which was maintained at 35° C by perfusing warm water between the walls of the cylinder. To measure the volume changes of the calf, a level meter was connected with the plethysmograph. The level meter was moved vertically to adjust the meniscus to the level of the subject's right atrium throughout the experiment.

A pressure of 180 mmHg (50–70 mmHg higher than the maximum arterial pressure of the subjects) was exerted on the surface of the calf segment within the plethysmograph through the pressure reservoir 1 (Fig. 1) for 2 min in order to collapse the blood vessels and to squeeze out blood from the calf segment. At the end of the 2 min period of compression, the calf volume was read on the level

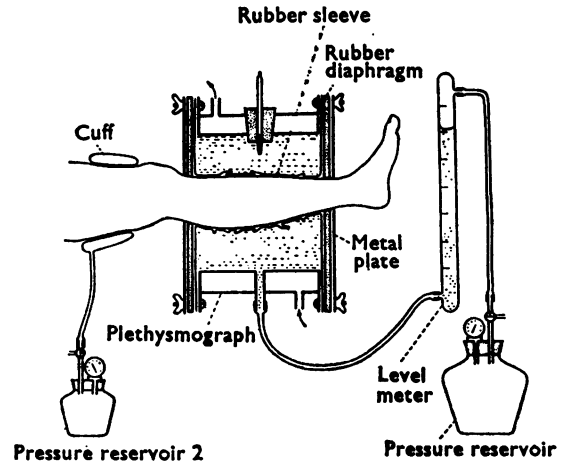

FIG. 1. Schematic drawing of a pressure plethysmograph applied to the human calf. Arrows indicate inlet and outlet of warm water circulating around the inner wall of the plethysmograph.

meter. This volume is referred to as ' reduced calf volume ' in the present paper. Immediately after determination of the reduced calf volume, the pressure was released.

Prior to application of venous congestion, successive measurements of the reduced calf volume were carried out at 4 min intervals. The reduced calf volume gradually decreased. After 3 or 4 measurements, however, the decrease in reduced calf volume per measurement became constant and was in the range 0·5–1·5 ml (0·03–0·10 ml/100 ml of calf tissue). This amount gave the volume of interstitial fluid which was pressed out of the calf segment by compression during each measurement. This volume was used for the correction, as adopted by Brown, Wise & Wheeler (1947), to evaluate the actual change in reduced calf volume due to congestion or smoking.

Venous congestion of the calf was produced by inflating a pneumatic cuff applied around the thigh (Fig. 1). The reduced calf volume was measured before and immediately after venous congestion of 15 min duration. The increase in reduced calf volume gave the amount of capillary filtration caused by the venous congestion. The rate of filtration was thus calculated in (ml/min)/100 ml of calf tissue. Such determinations of the rate of filtration were carried out with congestion pressures of 30, 40 and 50 mmHg. The rate of filtration increased linearly with the increase in congestion pressure, giving a regression line as shown in Figure 3. Capillary filtration coefficient was calculated from the slope of the regression line in terms of (ml/min)/100 ml of calf tissue per mmHg increase in capillary pressure, on the assumption that the elevation of capillary hydrostatic pressure is 80% of the elevation of venous congestion pressure (Pappenheimer & Soto-Rivera, 1948). Capillary filtration coefficient was determined before and after smoking

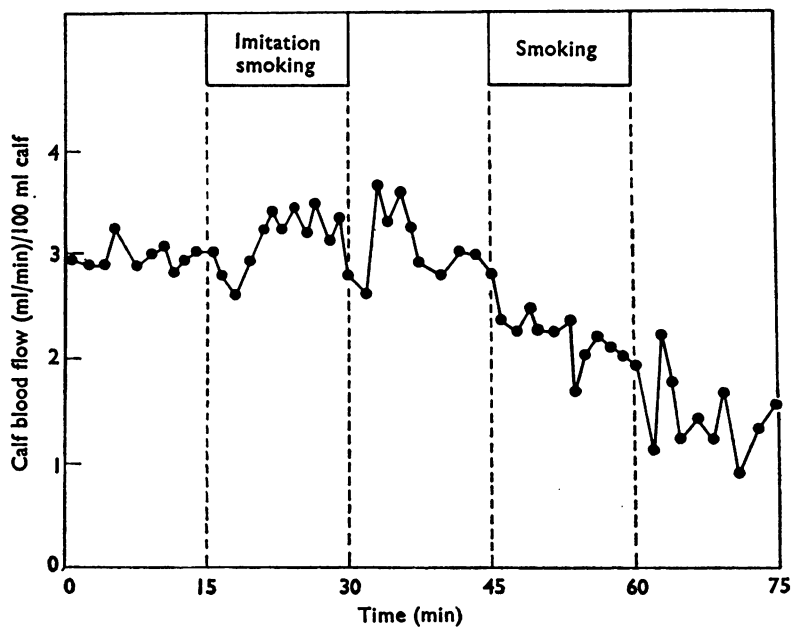

FIG. 2. Effect of imitation smoking and deep inhalations of cigarette smoke on calf blood flow. Subject T. Y.

which lasted 12–15 minutes. The venous congestion after smoking was produced for a 15 min period immediately after the cessation of smoking.

Blood flow in the enclosed part of the calf was measured by the venous occlusion method with the same apparatus. During the flow measurements, blood flow in the foot was occluded through a distal cuff placed at the ankle.

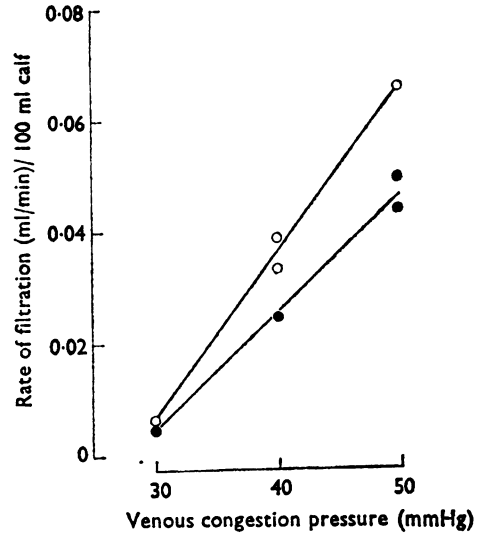

FIG. 3. Rate of filtration as a function of venous congestion pressure in the calf before (open circles) and after (closed circles) deep inhalations of cigarette smoke. Capillary filtration coefficient was calculated from the slope of regression line (see text). Subject K. T.

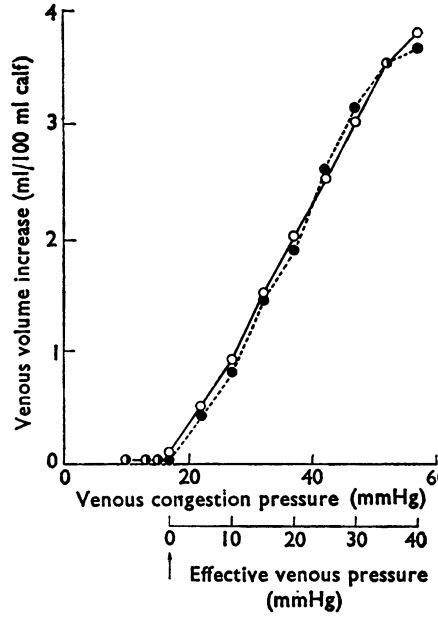

FIG. 4. Venous pressure–volume curve of the calf before (open circles) and after (closed circles) deep inhalations of cigarette smoke. Subject E. S.

As a measure of venous tone, relationships between changes of venous congestion pressure and the associated changes of volume of veins were studied according to the methods proposed by Wood & Eckstein (1958). Pressure in the cuff on the thigh was raised above atmospheric pressure by 1 mmHg increments until the first small increase in calf volume occurred. The cuff pressure required to produce this initial volume change is referred to as 'cuff zero'. From 'cuff zero', the cuff pressure was raised by 5 mmHg increments for a total of 40 mmHg. The increase in calf volume was measured for each cuff pressure and plotted in a 'venous pressure–volume curve' (Fig. 4). The venous volume (30) (i.e. the volume increase in ml per 100 ml of calf tissue with a rise in effective venous pressure of 30 mmHg) was obtained from the curve before and after smoking. Arterial occlusion at the ankle was maintained during the measurements of venous volume.

A standard brand of Japanese cigarette (Hi-lite) which gives 1·8 mg of nicotine when one cigarette is smoked (with a length of 30 mm left unsmoked at a frequency of one puff of 35 cc for 2 s per minute) was used. In some experiments the subject inhaled to his normal depth at intervals of 1 min, and this was regarded as a normal rate of smoking (Shepherd, 1951). These inhalations, however, were ineffective in causing vascular responses. Therefore a deep inhalation, repeated at intervals of 30 s, was used in most of the experiments. The inhalation was continued for 12–15 min and three cigarettes were smoked during this period. The actual smoking was preceded by a control period and a period of imitation smoking in which the deep inhalations were mimicked with an unlit cigarette. Measurements were taken during these periods to serve as control and reference.

Results

Effect of smoking on calf blood flow

When cigarette smoke was inhaled to a normal depth at intervals of 1 min for a period of 15 min, the calf blood flow remained substantially unchanged during and after the smoking. A marked gradual decrease in calf blood flow occurred, however, when deep inhalations of cigarette smoke were carried out at 30 s intervals for a period of 12–15 min (Fig. 2). The percentage decrease was calculated for each subject from the average flow in the control period of 15 min preceding the smoking and the average flow during the 15 min period after smoking (Table 1). The reduction in blood flow persisted for at least 45 min after the end of smoking.

TABLE 1. *Effect of smoking on calf blood flow and capillary filtration coefficient (CFC)*

Subject	Blood flow (ml / min × 100 ml of calf) Control	Blood flow (ml / min × 100 ml of calf) After smoking	Change in blood flow (%)	CFC (ml / min × 100 ml of calf × mmHg) Control	CFC (ml / min × 100 ml of calf × mmHg) After smoking	Change in CFC (%)
K. T.	3·2±0·3	2·2±0·3	−32	0·0038	0·0027	−29
T.Y.	3·8±0·4	2·1±0·5	−44	0·0033	0·0028	−15
E. S.	3·2±0·3	2·5±0·4	−22	0·0041	0·0035	−15
H. K.	3·6±0·4	2·7±0·4	−25	0·0039	0·0033	−15
means±SD	3·5±0·3	2·4±0·3	−31±10	0·0038±0·0004	0·0031±0·0004	−19±7

Each value of blood flow is mean±SD of 10 measurements.

During the period of imitation smoking, the level of calf blood flow fluctuated because of the deep breath taken at 30 s intervals, but no substantial change in the blood-flow level occurred. This observation showed that the decrease in calf blood flow during deep inhalations was caused by the cigarette smoke, not by the deep breath associated with the inhalation. These data on the effect of smoking and imitation smoking agree well with the report by Shepherd (1951) on hand blood flow.

Arterial blood pressure, measured on the brachial artery in a separate series of experiments, was increased only slightly by the deep inhalation of cigarette smoke in the same 4 subjects. If the mean values for the 4 subjects are taken, the systolic arterial pressure increased by 4 ± 3 mmHg and the diastolic pressure by 5 ± 3 mmHg. Assuming that the arterial pressure was substantially unchanged and that the venous pressure was unaffected by the smoking, vascular resistance in the calf was calculated to be raised 44% by inhalations, because the calf blood flow decreased by 31% ($1/(1{\cdot}00-0{\cdot}31)=1{\cdot}44$).

Effect of smoking on capillary filtration coefficient

Inhalations at 1 min intervals induced no change in capillary filtration coefficient. When the deep inhalations of cigarette smoke were carried out at intervals of 30 s for a period of 12–15 min, CFC decreased significantly. Typical data are shown in Fig. 3, where the relationships between the venous congestion pressure and the observed rate of capillary filtration are represented. The slope of the regression line is reduced by smoking, and this means a decrease in capillary filtration coefficient. Values of CFC obtained before and after the deep inhalation of smoke are listed on the right side of Table 1. The decrease in CFC was statistically significant ($0{\cdot}01<P<0{\cdot}02$).

Effect of smoking on reduced calf volume

If smoking induces a significant fall of the capillary hydrostatic pressure by increasing the vascular resistance of the precapillary region, capillary absorption of extravascular fluid (i.e. inward capillary filtration) is expected to occur, and this would be observed as a decrease in reduced calf volume. Therefore the effect of deep inhalations of smoke on the reduced calf volume was studied in the same 4 subjects. However, no change was observed during and after smoking except in one subject (T.Y.) who showed the capillary absorption of (0·009 ml/min)/100 ml of calf during the 15 min period immediately after smoking.

Effect of smoking on venous tone

A venous pressure–volume curve was obtained in the 4 subjects before and after deep inhalations of cigarette smoke (Fig. 4). No change in the pressure of 'cuff zero' was observed. Venous volume (30) was also unaltered. Venous tone seemed to be unaffected by smoking.

Discussion

Several studies have demonstrated that smoking reduces the limb blood flow of man (for a review see Shepherd, 1963) and this reduction does not occur in a sympathectomized limb (Rapaport, Frank & Massell, 1950). These findings indicate that the action of the vasoactive substance (nicotine) in cigarette smoke is

mediated by the sympathetic nerves innervating arterioles. The detailed mechanism of this action is generally believed to be that the nicotine absorbed via the lung acts peripherally on the terminals of sympathetic vasoconstrictor nerve and liberates noradrenaline from them (Burn, 1960, 1962), resulting in constriction of arterioles (resistance vessel). This view has been further supported by experiments (Fewings, Rand, Scroop & Whelan, 1966) which indicate that nicotine, injected arterially, decreases limb blood flow by stimulating sympathetic vasoconstrictor nerves, although the direct action of nicotine on vascular smooth muscle increases the blood flow subsequently.

Is the increase in vascular resistance, observed in the present study, solely attributable to arteriolar constriction? A part of the increase must be attributed to the decrease in number of parallel vascular circuits due to the closure of precapillary sphincters (sphincter vessel), since the decrease in capillary filtration coefficient suggests that the closure is actually occurring. If the whole of the increase (44%) in vascular resistance were attributable to arteriolar constriction, the ratio of precapillary resistance to postcapillary resistance would have increased from the control value of 4:1 (Pappenheimer & Soto-Rivera, 1948) to 6:1. Assuming that the mean pressure difference (about 100 mmHg) between artery and vein is little affected by smoking, the above increase in the ratio of pre- to postcapillary resistance would have reduced the capillary hydrostatic pressure by 6 mmHg, which would have caused an observable capillary absorption of (0·023 ml/min)/100 ml of calf when capillary filtration coefficient is assumed to be (0·0038 ml/min)/100 ml of calf/mmHg (mean control value of CFC, Table 1). On the contrary, if the closure of parallel circuits is contributing greatly to the observed increase in vascular resistance, the resistance-increase attributed to arterioles becomes much smaller, giving a minute drop in capillary hydrostatic pressure. Moreover the closure of the sphincter vessel will lessen the inward filtration by reducing the 'functional capillary surface area'. Thus the absence of capillary absorption, as was the case in most of the subjects, can be explained by assuming that a significant part of the observed increase in vascular resistance is due to the closure of precapillary sphincters.

The marked decrease in capillary filtration coefficient after smoking is the main finding of this study. The amount of decrease, however, was probably underestimated, since the CFC after smoking was slightly overestimated for the following reason. The calculation of CFC is based on the assumption that the rise in the capillary hydrostatic pressure is 80% of the rise in venous congestion pressure, and this assumption is based on the approximation that the ratio of pre- to postcapillary resistance is 4:1. This ratio must be increased by smoking since the arteriolar resistance rises while the venous tone is little affected. A given elevation of venous congestion pressure, therefore, causes a larger increase in capillary hydrostatic pressure after smoking than before smoking. This leads to an overestimation of capillary filtration coefficient after smoking, which results in an underestimation of its decrease due to smoking. However no correction for this underestimation was made, because the actual change in the ratio of pre- to postcapillary resistance was not precisely known, and because even a large change in the ratio affected the value of CFC only slightly (Celander & Mårild, 1962).

A decrease in capillary filtration coefficient must be due either to reduction of surface area of functioning capillaries, or to decrease in filtration constant of the

capillary wall, or to both of these factors. Reduction of capillary surface area seems to be most probable in the present experiments because the capillary wall itself is unlikely to be affected by smoking. Since capillary surface area is controlled by precapillary sphincters, the present result indicates that smoking induces their closure, thereby reducing the number of functioning capillaries. Closure of terminal arterioles also lessens the capillary surface, but this was not distinguished from the closure of precapillary sphincters in the present paper.

It seems most likely that the same mechanism as that seen in arteriolar constriction after smoking is also operating at the closure of precapillary sphincters, i.e. nicotine releases noradrenaline from the terminals of vasoconstrictor fibres which innervate precapillary sphincters. This view is supported by the observation that the smoking with inhalation to normal depth at 1 min intervals, which failed to reduce calf blood flow, also failed to reduce capillary filtration coefficient.

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