Effect of Cooling and of Smoking Tobacco upon the Blood Flow of Reactive Hyperemia of the Foot

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Tobacco smoking and body cooling have been shown to decrease the "resting" blood flow to the foot. The present study was designed to determine whether either of these 2 stimuli also affects the increased blood flow that follows a period of ischemia (reactive hyperemia). Blood flows to the foot were measured in subjects with and without vascular disease by the venous occlusion, water plethysmographic method in a warm and a cool environment before and during smoking. Patients with bilaterally and unilaterally sympathectomized limbs were also studied to determine the mechanism of the observed responses.

The peripheral vasoconstrictor effects of tobacco smoking or body cooling are well known and have been demonstrated by several observers.1-3 Recently, it has been shown in this laboratory that the smoking of 2 cigarettes produces a definite decrease of resting blood flow in the foot of approximately 90 per cent of subjects studied plethysmographically.4 This decrease in resting blood flow caused by smoking was less than that produced by a cool environment. The present investigation was designed to measure the effect of tobacco smoking and body cooling on the peripheral circulation during one condition of increased need namely the increase of blood flow following a period of ischemia of a limb, commonly referred to as reactive hyperemia blood flow.

Method
Measurements of foot blood flow were obtained by the venous occlusion plethysmographic method on patients with and without vascular disease. The subjects, who varied in age from 16 to 72 years, were habitual smokers. Studies were performed in a constant temperature room with the lightly clothed subject in the supine position. The subject's slightly elevated foot and ankle were enclosed in the Wahmann Foot plethysmograph filled with water at a temperature of 89 F., in both the warm (83 F.) and the cool (68 F.) environment. This position brought the posterior aspect of the lower leg and foot approximately to heart level. The techne used for enclosing the foot in the water plethysmograph has been previously described in detail.4 The water level within the plethysmograph produced a hydrostatic pressure equal to or slightly greater than natural local venous pressure.6 Inflation of a 13-cm. wide blood pressure cuff applied at the ankle just proximal to the plethysmograph produced the venous occlusion necessary to measure blood flow. Arterial occlusion was produced by inflating a similar cuff applied 3 cm. below the knee. The rate of change of foot volume was recorded by means of a volume calibrated Brodie bellows. The lowest venous occlusion pressure required to obtain the maximum rate of increase in foot volume was determined at the beginning of each experiment and averaged 41 mm. Hg. This pressure was then used throughout the experiment. Arterial occlusion pressure was set at 50 mm. Hg above the patient's systolic blood pressure as measured in the arm by the auscultatory method. Leakage of blood from the arteries into the foot beneath the cuff could be detected by a rise in volume of the foot during the occlusion period. The volume of foot within the plethysmograph was determined after the experiment by displacement. A thermocouple was applied to the tip of the opposite great toe for measuring skin temperature.

The general protocol of each experiment is illustrated in figure 1. The patients were acclimated to room temperature (warm and cool) for at least 1 hour and for whatever additional time was required to obtain relatively constant blood flow and skin temperature measurements. Then 3 resting blood flows were obtained every 5 minutes for 15 minutes. The mean resting blood flow for this period is plotted in figure 1. Arterial occlusion of 5 minutes' duration, indicated by zero flow, was then applied. Following release of arterial occlusion, blood flow measurements were repeated at 15-second intervals for 2 minutes and then at 30-second intervals for a further 6 minutes. Another

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series of resting blood flows was obtained as described above. The subject then smoked 2 regular type cigarettes at his own rate, requiring about 14 minutes. (No king size, low nicotine, or filtered cigarettes were used.) Five minutes after smoking began, arterial occlusion was reapplied and the previous observations were repeated. Blood flow to the foot was expressed in milliliters per minute per 100 ml. of foot tissue.

It was necessary to select a single time period for the reactive hyperemia phase in comparing data from different experiments. Vasodilatation usually persisted for at least 2 minutes; almost invariably the total duration of control reactive hyperemia was the same as or longer than its paired smoking reactive hyperemia (in 50 of 55 pairs). Therefore, the 2-minute period was selected and is indicated by the dotted lines in figure 1. By means of a planimeter, it was then possible to measure the total area within each curve and convert this mathematically to ml. per 100 ml. of foot tissue. The value obtained was the volume of blood that had passed through 100 ml. of foot tissue during the 2-minute period that followed release of the arterial occlusion. It will be referred to hereafter as RHBF (reactive hyperemia blood flow). In subject number 3 (fig. 1) this value was 15.4 ml. before smoking and 7.8 ml. during smoking.

The spontaneous variation of RHBF without smoking was investigated by measuring RHBF repeatedly under the standard experimental conditions described above.

Results

I. Variation of RHBF

As shown in figure 2, 3 RHBFs in the warm, and 3 in the cool environment were determined on 6 subjects; data were obtained on 2 more subjects in the warm room only. The greatest variation among subjects who showed a RHBF less than 26 ml. per 100 ml. of foot tissue was 3.5 ml. Therefore only changes in RHBF greater than this value were considered to be of importance. One other subject had cirrhosis of the liver (patient 24) associated with an exceptionally high RHBF. The variation of RHBF was greater in this subject than that of the above group (6.7 ml.).

II. Warm Room Experiments

Figure 3 shows the RHBFs before smoking and during smoking in the room at 83 F. in 27

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Fig. 1 Top. The experimental protocol and method of calculating reactive hyperemia blood flow.

Fig. 2 Middle. The variability of reactive hyperemia blood flow with repeated determinations on the same subject without smoking, in a constant temperature environment.

Fig. 3 Bottom. The effect of smoking upon reactive hyperemia blood flow in warm and cool environments. The upper panel is composed of those subjects considered to have had significant decreases in reactive hyperemia blood flow; the lower panel, those subjects with insignificant changes.

Figures
EFFECT OF COOLING AND SMOKING ON BLOOD FLOW

The figure shows 12 subjects in whom the RHBF remained the same, increased, or decreased by less than the variation described above. The 27 control RHBFs averaged 18.0 ml per 100 ml of foot tissue (6.3 to 79.3 ml). The 27 RHBFs during smoking averaged 13.7 ml per 100 ml of foot tissue (3 to 81.2 ml).

III. Cool Room Experiments

Figure 3 also shows the RHBFs before smoking and during smoking in the room at 68 F. in 14 experiments. Smoking produced a definite decrease in RHBF in 6 of the 14 studies. Repeat experiments performed on different days show comparable responses in both subjects (number 23 and number 20). In the cool room experiments 14 control RHBFs averaged 13.6 ml (5.5 to 52.0 ml), while 14 RHBFs during smoking averaged 9.9 ml per 100 ml of foot tissue (1.3 to 51.2 ml).

IV. Comparison of Control Warm and Cool Room RHBFs

Figure 4 demonstrates the decrease in RHBF produced by cooling the environment. Of the 17 experiments, 14 showed a definite reduction of RHBF by cooling from 83 to 68 F. Subject number 23 showed comparable responses on 2 different days. Following cooling, subject number 20 had a greater decrease in RHBF in his right foot after his left leg had been sympathectomized. The 17 RHBFs in the warm room averaged 19.9 ml (9.9 to 79.3 ml) while the 17 RHBFs in the cool room averaged 12.6 ml per 100 ml of foot tissue (4.7 to 52.0 ml).

V. Experiments on Sympathectomized Patients

Seven sympathectomized legs of 6 patients were studied in both the warm and cool environment as shown in Figure 5. In the room at 83 F. smoking produced no change in the RHBF. The control RHBFs averaged 17.0 ml while the RHBFs during smoking averaged 17.5 ml. Two of the 7 studies in the 68 F. room showed a decrease of RHBF during smoking (subjects 21 and 30). The 7 control

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**Figure 4** Top. The effect of cooling the environment upon reactive hyperemia blood flow. The upper panel is composed of those subjects considered to have had significant decrease in reactive hyperemia blood flow; the lower panel, those subjects without significant change.

**Figure 5** Bottom. The effect of smoking in the warm environment (upper panel), smoking in the cool environment (middle panel) and of the cool environment, compared with the warm environment (lower panel) upon reactive hyperemia blood flow of sympathectomized limbs.

experiments. The upper half of the figure shows 15 studies in which smoking reduced the RHBF. Two experiments on separate days were performed on subject number 5 and showed comparable responses. Subject number 20 showed no response to smoking in his right foot until after his left limb had been sympathectomized. The lower half of
RHBFs in the cool room averaged 15.4 ml. while the 7 RHBFs during smoking averaged 13.3 ml. Cooling from 83 to 68 F. produced no reduction in RHBF in 5 of the 7 sympathectomized limbs; the RHBFs averaged 16.4 and 14.7 ml. in the warm room and in the cool room, respectively. (The small blood flows of subject number 22 presumably were due to thromboangiitis obliterans.)

Four of these patients had unilateral lumbar sympathectomies and were studied with simultaneous blood flow measurements of both feet by means of 2 plethysmographs. Except for the additional plethysmograph the same procedure as described above was used. The sympathectomized feet showed no change in RHBF during smoking in the 8 warm and cool room studies; the unsympathectomized feet showed a definite reduction of RHBF during smoking in 6 of the 8 experiments (fig. 6).

Fourteen of the 27 subjects were considered to have peripheral vascular disease that was vasospastic in origin. There was no apparent accentuation of the response to smoking or to cooling in these 14 patients. There were 10 subjects with normal circulation, 3 subjects with mild arteriosclerosis obliterans, 1 subject with severe arteriosclerosis obliterans, and 1 subject with thromboangiitis obliterans. Two patients (subjects number 16 and 24) had increased peripheral circulation associated with cirrhosis of the liver and 1 patient had terminal vessel occlusions in the toes due to a secondary polycythemia.

**Discussion**

Total reactive hyperemia blood flow presumably includes the blood flow through arteriovenous shunts as well as blood flow through nutrient capillaries of the foot. A portion of the capillary blood flow supplies resting metabolic needs of the tissue, a portion meets the unsupplied metabolic needs of the previously ischemic tissue, and a portion may be metabolically superfluous. Despite the possibility of such varied metabolic and nonmetabolic routes of reactive hyperemia blood flow, a reduction of this total flow by reflex vasoconstrictor stimuli would suggest that those stimuli prevented the tissue metabolic requirements from being satisfied as efficiently as before. While this result might be of little consequence to an individual with a normal circulation, it conceivably would be important to a patient with advanced peripheral vascular disease. The action of such reflex vasoconstrictor stimuli on reactive hyperemia blood flow has not been investigated previously but it has been mentioned briefly in connection with peak blood flows in the toe. In the present study the vasoconstrictor effects of tobacco smoking and of reflex body cooling on reactive hyperemia of the foot (which is predisposed to the complications of occlusive vascular disease) have been investigated.

It has been shown by other workers that smoking produces a decrease in skin temperature. Since changes in local temperature affect reactive hyperemia, probably as a result of altered local metabolic requirement, the water in the foot plethysmograph was maintained at a constant 89 F. In this manner, the effects of smoking or of a cool body environment were not influenced by changes in water temperature surrounding the foot.

Reactive hyperemia is often reported in terms of the blood flow in excess of mean rest-
EFFECT OF COOLING AND SMOKING ON BLOOD FLOW

ing blood flow. However the blood flow in the foot is quite variable, particularly during smoking, as has been previously shown. For this reason, it would be difficult to predict the mean resting blood flow that would have been present had no arterial occlusion been performed. Therefore, the total postischemia blood flow was considered to be a more objective measurement. In so far as possible, the data were also calculated to determine the blood flow in excess of presumed resting blood flow. Mean blood flow immediately following the reactive hyperemia phase was used as the resting blood flow. The effects of smoking and body cooling upon reactive hyperemia were qualitatively the same, regardless of the method of calculation, with few exceptions.

In the studies of the variation of the measurement of RHBF, the first determination in 5 experiments in the warm room was less than the second or third RHBFs. Eichna and Wilkins11 and Patterson and Whelan12 have pointed out that the peak or maximal blood flow obtained during reactive hyperemia is lower in the first than in the subsequent 2 or 3 of a series but then becomes remarkably constant in the forearm. The latter authors did not find that this phenomenon of “augmentation of successive flows” applied to the total reactive hyperemia blood flow calculated as the excess over resting blood flow, but the present figures differ from those in that the present ones give the total postischemia blood flow to the foot. There was no consistent tendency for the foot RHBF so calculated to decrease in either the warm or the cool environment during the course of the present experiments.

In 15 of 27 warm (83 F.) room, and in 6 of 14 cool (68 F.) room experiments, the smoking of 2 cigarettes decreased the RHBF to the foot. These patients also showed a decrease in skin temperature as measured in the contralateral foot, averaging 5.7 F. and ranging from 1.5 to 11 F.

In 14 of 17 experiments, it was demonstrated that cooling the environment from 83 to 68 F. definitely decreased RHBF of the foot although the water temperature in the plethysmograph was maintained constant at 89 F. These studies show that smoking may reduce the total amount of blood flow to a previously ischemic foot in certain individuals, but that body cooling is the more consistent stimulus in this regard. The decrease of RHBF of the foot by body cooling does not necessarily prevent a further reduction by smoking, as was demonstrated by 5 of our subjects. This would suggest that these 2 stimuli may be at least additive.

In many of the subjects in these studies, smoking or cooling also produced a lower level of resting blood flow. However, there was no apparent correlation between the degree of reduction of RHBF and the degree of reduction of resting blood flow during these vasoconstrictor stimuli.

The experiments performed on patients with lumbar sympathectomies indicate that smoking and body cooling exert their effect upon reactive hyperemia via the sympathetic nervous system rather than through the direct action of nicotine or other circulating substances upon the blood vessels. This indication is supported particularly by the studies of patients with unilateral lumbar sympathectomies, who responded to the stimuli in the unsympathetomized foot but not in the sympathectomized foot. In this connection, in simultaneous studies on both feet Landowne and Katz13 have shown that the blood flow in an extremity is not significantly affected by performing a reactive hyperemia measurement in the contralateral limb. We also observed on one patient (subject 20) that a unilateral sympathectomy resulted in an increased reactivity in the opposite extremity as compared with its presympathectomy responses.

Summary

The effects of tobacco smoking and of body cooling on the increase in total blood flow that follows a period of ischemia (reactive hyperemia blood flow) of the foot were studied by venous occlusion, water plethysmography.

In 15 of 27 warm (83 F.) and 6 of 14 cool (68 F.) room experiments, the smoking of 2
cigarettes decreased the reactive hyperemia blood flow of the foot. In 14 of 17 studies, cooling the environment from 83 to 68°F, definitely decreased reactive hyperemia blood flow of the foot and appeared to be a more consistent stimulus than smoking in reducing reactive hyperemia. These studies also demonstrated that smoking and body cooling may have additive effects in reducing reactive hyperemia.

Experiments on patients with sympathectomized limbs showed that the above observed responses were mediated through the sympathetic nervous system. This was confirmed by the study of patients with unilateral sympathectomy who showed no decrease in reactive hyperemia blood flow in the sympathectomized foot during smoking but a definite decrease in the concomitantly studied unsympathectomized foot during smoking.

**SUMMARY IN INTERLINGUA**

Le effecto de fumar tabaco e de frigidar le corpore super le augmento del fluxo de sanguine total che occurrent post un periodo de ischemia (fluxo sanguine de hyperemia reactive) esseva studiate in le pede per medio de hydroplethysmographia sub conditiones de occlusion venose.

In 15 ex 7 experimentos in ambientes a temperatura elevate (83°F) e in 6 ex 14 experimentos in ambientes a temperatura reducide (68°F), le fumar de 2 cigaretas reduciva le fluxo de sanguine per hyperemia reactive in le pede. In 14 ex 17 experimentos, reducere le temperatura del ambiente ab 83 a 68°F effeetuavan un definite reduction del fluxo sanguine per hyperemia reactive in le pede. Il pareva que reducere le temperatura esseva plus constante che fumar tabaco in su effecto depressori super le hyperemia reactive. Le studios etiam indicava que fumar tabaco e frigidar le corpore exercise possibilemente effectos additive super le hyperemia reactive.

Experimentos in patientes con extremitates sympathectomisate monstrava que le supra-mentionate responsas es mediate per le sistema nervose sympathetic. Isto esseva confirmate per le studio de patientes con sympathectomia unilateral in qui fumar tabaco resulta in nulle reduction del fluxo sanguine per hyperemia reactive in le pede sympathectomisate sed (in observationes concomitante) un definite reduction de ille fluxo in le pede non sympathectomisate.

**REFERENCES**

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