The Effect of Smoking upon Blood Flow in the Sympathectomized Limb

By Samuel I. Rapaport, M.D., Hugh A. Frank, M.D., and Theodore B. Massell, M.D.

The effect of smoking upon the blood flow of a sympathectomized limb was examined in 19 patients. Sympathectomy was found to abolish the peripheral vasoconstriction produced by smoking. The constriction, therefore, is mediated by sympathetic vasomotor fibers and not by humoral agents such as adrenaline or posterior pituitary hormone. There is no difference in the response of patients sympathectomized for thromboangiitis obliterans, arteriosclerosis or severe vasospasm. The relation between the vasoconstrictor effect of smoking and the action of tobacco in thromboangiitis obliterans is discussed.

The peripheral vasoconstriction produced by smoking has been known for many years. Most investigators1-5 have found this constriction due to the action of the absorbed nicotine; and not, as some have claimed,6-7 the result of sympathetic reflexes initiated by the breathing pattern of smoking or by the irritation of the smoke itself. Goetz8 reported that the constriction at the very onset of smoking is of such reflex origin, while the more marked decrease in blood flow which follows is due to the sympathomimetic action of the absorbed nicotine.

Nicotine in the amount inhaled from one or two cigarettes acts as a general synaptic stimulant. As such, in theory, it could produce peripheral vasoconstriction by four known mechanisms: (1) by the excitation of central vasomotor centers, (2) by a direct stimulation of sympathetic ganglia, (3) by an increased production of adrenaline, and (4) by the liberation of posterior pituitary hormone. The first two of these mechanisms require an intact sympathetic nerve supply to the blood vessels. The third and fourth are humoral and should not be abolished by sympathectomy. Rather, sympathectomy has been said to increase the sensitivity of blood vessels to the vasoconstrictor effects of adrenaline,9,10 although this is questionable.11 About 50 milliliters of posterior pituitary hormone are said to be liberated by the smoking of one or two cigarettes.12 This is the equivalent in man of the amount found to decrease coronary blood flow in the dog. It seemed possible that it should also produce peripheral vasoconstriction.

The present experiments were conducted to answer the question—does the vasoconstrictor response to smoking persist after sympathectomy, i.e., is its mechanism nervous or humoral? This question has clinical as well as theoretic interest. While it is generally recognized that tobacco accelerates the disease process of thromboangiitis obliterans, the manner in which it does so is unknown. There are observations to suggest that it is unrelated to vasoconstriction. In the first place, while there is a marked individual variation in the degree of vasoconstriction produced by smoking, there is no clear cut distinction between normal smokers and patients with thromboangiitis obliterans.5,13-15 Secondly, Abramson and his co-workers16 have shown that the vasoconstriction of smoking is limited to the skin. Blood flow through muscle is not reduced. Yet muscle vessels are also involved in the thromboangiitis process.

There are recent reports in which the failure of sympathectomy to afford relief in a small percentage of patients with thromboangiitis obliterans has been attributed to continued smoking. Freeman17 described good results from
sympathectomy in 16 patients who stopped smoking but not in 3 who continued to smoke. In a recent panel on peripheral vascular disease there was general agreement that smoking after sympathectomy resulted in a progression of the disease. If tobacco can continue to exert its pernicious effect in this disease in the sympathectomized limb, it seemed important to determine whether or not vasoconstriction could also be demonstrated in such a limb.

The data in the literature on the response to smoking after sympathectomy are scanty and conflicting. Maddock and Coller could not demonstrate vasoconstriction on the operated side in a patient with a cervidorsal and lumbar sympathectomy for Raynaud’s disease. They also observed in 2 patients that sympathetic nerve block with procaine eliminated the constriction. However, the sensitivity of blood vessels after the removal of sympathetic control changes with time, and it is not safe to assume that a response observed acutely following a sympathetic block will persist after sympathectomy. These and Freeland reported the opposite—a patient with an upper thoracic sympathectomy for Raynaud’s disease in whom smoking produced a sharp decrease in skin temperature. They offered no evidence to exclude the possibility of regeneration, a point of particular concern in upper thoracic sympathectomy. Goetz stated that vasoconstriction was delayed but not abolished after sympathectomy.

We have observed the effect of smoking upon skin temperature and blood flow in 18 patients after lumbar sympathectomy and one patient after an upper thoracic sympathectomy. Six of these had arteriosclerosis obliterans, 6 had thromboangiitis obliterans, while 7 were operated on for severe vasospasm. They were so chosen to evaluate any differences due to the underlying disease process. The elapsed time between surgery and the experiment varied from 4 days to 26 months. In some patients L-3 was the lowermost ganglion removed, while in others L-4 was also excised. In the latter the postganglionic fibers to the second toe, the toe whose blood flow was measured, may have been interrupted.

Experimental Procedure

The test was performed in the early afternoon. The patient went without lunch and did not smoke for several hours. No medication was given during that day, and no sedation the night before. All of the subjects had been habitual smokers, although several had stopped some months earlier. An attempt was made to start the experiment with the room temperature about 80 F. Usually it was impossible to prevent a variation of room temperature of one or two degrees during the test. However, this was not felt to be a source of error, since the sympathectomized limb is not subject to changes in blood flow produced by thermal reflexes.

The patient, clad in light pajamas, rested quietly in the supine position. Thermocouples were attached to the big toe of each foot and to a forefinger. A fourth thermocouple measured room temperature. Temperatures were recorded in rotation, one each minute, upon a Leeds and Northrup self-balancing potentiometer (Micromax). Pulse volume and blood flow measurements were taken from the second toe of the sympathectomized foot by the use of a Burch-Winsor pneumoplethysmograph. A 5 cc. volume of toe was measured by displacement of an aqueous solution of gentian violet. The plethysmograph cup was then fitted to the stained portion of the toe and an air-tight seal between the cup and toe was made with a nonhardening calking compound (Kalkkord).

Blood flow was measured by the venous occlusion method as described by Goetz. The occlusion cuff was placed at the ankle and a pressure of 45 mm. Hg was applied suddenly from a reservoir. Since, in our experience, the “straight line” portion of the rise after venous occlusion is often very short, a line drawn tangent to that portion of the curve, at least 2 pulse beats in length, which showed the maximum rise was taken as the best approximation of blood flow. The values so obtained were multiplied by 3 to correct for the placement of the cuff at the ankle instead of the base of the toe, and are expressed in cc. per minute per 100 cc. of part.

At the beginning of each experiment the completeness of sympathectomy was checked by the immersion of one hand in ice water for one minute. This results in a sudden reflex fall in pulse and part volume in the intact digit, but not in a sympathectomized digit. In every instance the temperature of the sympathectomized extremity was considerably above that of the opposite extremity and above room temperature.

The patient rested at least 30 minutes after the cold immersion test before beginning to smoke. During this period from two to eight blood flow determinations were made. In most, three blood flow measurements were made at one to two minute intervals 15 and 30 minutes after the cold immersion. Blood pressure and pulse rate were recorded.
The patient was then allowed to smoke two cigarettes in succession. He was instructed to inhale but otherwise was permitted to smoke in his own manner. The pulse volume was recorded continuously except when venous occlusion measurements were being made. In some experiments these were taken after each cigarette and 15 to 20 minutes after smoking. In others, venous occlusion measurements were taken every two minutes during the period of smoking and again 15 to 20 minutes later. Blood pressure was noted just before or just after each venous occlusion.

RESULTS AND DISCUSSION

Without exception the skin temperature of the sympathectomized limb did not fall during or after smoking. This is illustrated in figure 1, which is a graph of the temperature response of a sympathectomized toe and of an intact finger and toe. The room temperature was 81 F. and the sympathectomized toe stayed between 94.5 and 95 F. Its temperature was not altered by immersion of one hand in ice water or by smoking. The finger tip, the vessels of which were fully dilated, did not change in temperature when the opposite hand was immersed in ice water. However, when smoking was started there was a sharp drop in finger tip temperature. The temperature of the intact toe was rising when the hand was immersed. A prompt fall resulted which continued for about 20 minutes. The fact that cold immersion produced a fall in toe but not in finger temperature is an illustration of the general rule that the effect of any stimulus upon arteriolar tone is modified by the pre-existing state of the vessels. Vessels which are between constriction and full dilatation often show a marked response to vasoconstrictor stimuli which will evoke only a transitory response from fully dilated vessels. When the intact toe temperature began to rise again the subject was permitted to smoke. There was a second sharp fall in skin temperature which persisted until the experiment was stopped.

The skin temperature records of the other patients were similar to this example in so far as the sympathectomized limb is concerned. As expected, arteriolar constriction in the intact extremity during smoking was manifested by a drop in skin temperature of from 1.5 to 11 F. In a few instances the skin temperature of the intact extremity prior to smoking approached that of the room. In the presence of this degree of vasoconstriction no further constriction during the period of smoking could be demonstrated by the skin temperature method.

The plethysmographic tracings demonstrate that blood flow in the sympathectomized digit is not diminished by smoking. Figures 2 and 3 show the type of pulse volume and venous occlusion tracings which were obtained; and the failure of smoking to decrease the venous occlusion slope. These tracings also illustrate the fact that the pulse volume deflection is not necessarily a measure of the rate of blood flow. In figure 2 there is a large pulse deflection while in figure 3 it is practically indistinguishable. Yet the blood flow rates in the 2 patients are within the same range. The pulse volume deflection is a measure of the difference between arterial inflow and venous outflow throughout the pulse cycle. In the first patient the large vessels are patent, and with each heart beat most of the blood enters the toe rapidly over a short period of time. The large vessels of the second patient are sufficiently occluded by arteriosclerotic plaques to prevent a rush of blood into the toe with systole. Although a large amount of blood is provided the toe through the small collateral vessels opened by sympathectomy, the flow through these vessels is slower and more evenly distributed throughout the pulse cycle. At no time during the cycle is there a large difference between the rate of arterial inflow and venous outflow; hence, the pulse volume deflection is small.

Moreover, figure 2 illustrates a common find-
a decrease in pulse volume without a corresponding reduction in blood flow. (Compare control tracing with that after the second cigarette.) The reason for this is not completely understood. It appears to depend in part upon a corresponding increase in heart rate which damps fluctuation by decreasing both the stroke volume and the venous emptying between beats. It would seem that when there is a change in heart rate, such as the increase of 5 to 20 beats per minute which occurs during smoking, change in the height of the pulse volume must be interpreted with care.

The individual blood flow measurements and their averages are listed in table 1. In this table the abbreviations AO, TAO, and Vspm refer to arteriosclerosis obliterans, thromboangitis obliterans and vasospasm, respectively. The time between sympathectomy and the experiment is listed to the nearest day, week or month. Under the heading level of sympathectomy the upper and lowermost ganglia removed are tabulated. These levels were confirmed by roentgen visualization of dura clips placed at operation. Room temperature is abbreviated as R.T. Blood flow is in cc. per minute per 100 cc. of tissue. Control blood flows are at 15 and 30 minutes after the cold immer-

Fig. 2. Subject J. W. Pulse volume tracings are shown in the left hand column; venous occlusion tracings on the right. For details see text.

sion test. Under the headings 1st and 2nd are listed the blood flow measurements taken either during or immediately after each cigarette. The averages are given in separate columns. These data show that smoking did not decrease blood flow in 18 of 20 experiments. The 2 exceptions, V. W. and A. H., appeared clinically to have been completely sympathectomized, but in each, vasomotor reflexes were demonstrated. For example, patient V. W. had a
toe temperature on the operated side of 92°F, while on the unoperated side the temperature of the toe was that of the room, 77°F. Yet, as shown in figure 4, immersion of one hand in ice water produced a transient reflex vasoconstriction in the supposedly sympathectomized toe. This indicated that some sympathetic fibers were still intact; the fall in blood flow which occurred during smoking could have been the result of their stimulation. Such a case remaining 18 experiments are summarized in figure 5. In this graph the blood flow 15 minutes after cold immersion has been given a value of 100 per cent. Subsequent readings are expressed in per cent of this. The scatter graph shows the distribution of blood flow for the individual patients, the bar graph the averages for the group. Since the error in blood flow measurement in our hands was approximately 20 per cent, the small apparent increase in blood flow points out the necessity of establishing the completeness of sympathectomy by an attempt to elicit vasomotor reflexes. It is also of interest in that a diminution in blood flow of over 40 per cent during the period of smoking was not accompanied by a drop in skin temperature. This illustrates the insensitivity of skin temperature as an index of blood flow in the room temperature range, a point emphasized by Fetcher.26

The average blood flow measurements of the during and after smoking is not statistically significant. Yet it is conceivable that flow does actually increase in the sympathectomized vascular bed as the result of vasoconstriction in unsympathectomized areas, and of the small rise in blood pressure which occurs (average systolic increase 9 mm., average diastolic 4 mm. Hg). In any event, the apparent increase makes it unlikely that any real decrease could have been masked by experimental error.

These observations demonstrate that the
<table>
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<th>Subj.</th>
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<th>R.T.</th>
<th>Blood Flow cc./min./100 cc.</th>
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Table 1.—Continued

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<td>Vspm</td>
<td>11d</td>
<td>L2-L4</td>
<td>77-81</td>
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<td>L2-L3</td>
<td>78-80</td>
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<td>L2-L3</td>
<td>82-84</td>
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<td>L2-L4</td>
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<td>25 20 36 29 29</td>
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<td>11m</td>
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Fig. 4. Effect of immersion of one hand in ice water (first white marker) on the pulse volume tracing of a toe in two patients. The upper tracing shows the response in an incompletely sympathectomized extremity. The lower tracing shows the lack of response when sympathectomy is complete.

vasoconstrictor effect of smoking requires an intact sympathetic nerve supply to the blood vessels. It is not due to humoral mechanisms such as increased adrenaline production or liberation of posterior pituitary hormone. There is no difference in the response of patients sympathectomized for thromboangiitis obliterans, arteriosclerosis obliterans, or severe vasospasm. Neither the time elapsed since surgery, nor the type of surgery, i.e., whether or not L-4 ganglion is removed, appears to affect the result.
The fact that the 6 patients with thromboangiitis obliterans exhibited the same lack of vasoconstriction as did the others, does not invalidate the clinical reports that smoking continues to be harmful in this disease in the sympathectomized limb. Nor should it be made the basis for permitting patients to smoke after sympathectomy. Rather, it is additional evidence that the harmful effect of smoking in thromboangiitis obliterans is not the result of the vasoconstrictor action of nicotine.

Summary

The effect of smoking upon the skin temperature and blood flow of a sympathectomized limb was examined in 19 patients. Sympathectomy was found to abolish the peripheral vasoconstriction produced by smoking. This constriction, therefore, is mediated by sympathetic vasomotor fibers and not by humoral agents such as adrenaline or posterior pituitary hormone. There is no difference in the response of patients sympathectomized for thromboangiitis obliterans, arteriosclerosis or severe vasospasm. These results are of clinical interest because of recent reports in which continued smoking has been suggested as the reason for the failure of sympathectomy to afford relief in some patients with thromboangiitis obliterans. For, if tobacco can aggravate the thromboangiitic process in a sympathectomized limb, the implication exists that the mechanism of its pernicious effect in this disease is independent of its known vasoconstrictor action in the intact limb.

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Bibliography

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