Blood Flow in the Human Calf during Tobacco Smoking

By Jay D. Coffman, M.D., and Stanley L. Javett, M.D., B.Ch.

The cutaneous vasoconstrictive effect of tobacco smoking has been demonstrated by several groups. In about 50 per cent of people, smoking has been reported to diminish the increase in foot blood flow, called reactive hyperemia, which follows a period of arterial occlusion. Experiments on patients with sympathectomized limbs showed that the decrease in reactive hyperemia was mediated through the sympathetic nervous system. Few studies are available concerning the effect of tobacco smoking on skeletal muscle blood flow. Abramson et al. found no change or very small increases in plethysmographic forearm blood flows during cigarette smoking. Formerly, it was considered that the plethysmographic blood flow measurements in the calf or forearm were actually representative of muscle flow because the ratio of skin to muscle in these areas was small. However, Cooper and his co-workers have shown, by using the technic of adrenalin iontophoresis to stop cutaneous blood flow, that the skin may under certain conditions account for as much as 60 per cent of the resting forearm blood flow. Employing a plethysmograph, it is apparent that increases in muscle blood flow may be hidden or exaggerated by changes in skin flow. Therefore, the effect of tobacco smoking was investigated using the disappearance rate of a radioisotope from skeletal muscle as a measure of its capillary blood flow.

Methods

Total calf blood flows were measured in one leg by means of venous occlusion plethysmography on lightly clothed subjects lying in the supine position. The subject's leg was slightly elevated and the calf enclosed in a plethysmograph filled with water (10 cm. above the calf) at a temperature of 34 C. This position maintained the posterior aspect of the lower leg approximately at heart level. The technic for enclosing the limb in the water plethysmograph has been described previously in detail. The foot was excluded during flow measurements by an 8-cm.-wide pneumatic cuff on the ankle inflated to 50 mm. Hg above the subject's systolic blood pressure as measured in the arm by the auscultatory method. A second pneumatic cuff, 13 cm. wide, was placed just above the knee proximal to the plethysmograph. Inflation of this cuff produced the venous occlusion necessary to measure blood flow. The lowest venous occlusion required to obtain the maximum rate of increase in calf volume was determined at the beginning of each experiment and averaged 23 mm. Hg. Water level fluctuations were detected by a Sanborn displacement transducer which senses the vertical motion of a lucite float 4 inches in diameter. The transducer was used in conjunction with a Sanborn strain-gage amplifier and a direct-writing recorder. The recording system was calibrated at the beginning and end of each experiment by introducing known quantities of water into the plethysmograph. The volume of the calf within the plethysmograph was determined after the experiment by measurement of the water displaced.

The disappearance rate of a radioisotope from a lateral calf muscle of the other leg was used as an indication of skeletal muscle capillary blood flow. An injection of 0.1 ml. of NaI in saline was made with a 26-gage 5/8-inch needle approximately 3 inches below the head of the fibula; the needle was inserted to its hub in an attempt to control depth of injection. The disappearance rate was monitored by a shielded scintillation probe, ratemeter, and linear recorder. The scintillation probe contained a 1-inch by 1-inch-thick sodium iodide crystal, thallium activated. The dose of NaI varied from 3 to 10 μc. Disappearance rates were plotted on semilogarithmic paper after subtraction of the background counts. Disappearance rates are expressed by the clearance constant, K, which is the natural logarithm of 2 divided by the half-time of the disappearance rate

\[
K = \frac{0.693}{1/2t}
\]

An increase or decrease in the

\[K \neq \frac{0.693}{1/2t}\]

**Footnote:** R.E.A.C. Model H580. Time constant set at 10 seconds.

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clearance constant or rate would indicate a rise or fall in capillary blood flow. Radial pulse rates and sphygmonanometric blood pressure determinations were followed every 5 minutes. Calf and toe skin temperatures were measured with a thermocouple.

Subjects rested in a supine position at a constant room temperature of 78 to 83 F for 45 to 60 minutes before the test. After a 15-minute period of control plethysmographic flow measurements and about 10 minutes of radioactive counts to demonstrate that the disappearance rate was linear, the subject smoked 1 or 2 regular-size, nonfiltered cigarettes. Seventeen normal male subjects (average age of 28 years), 4 patients with sympathectomized limbs, and 6 patients with arteriosclerosis obliterans were tested. Four of the normal subjects were retested at another time. NaI\textsuperscript{131} disappearance curves were also performed on 8 of the normal subjects without smoking during a separate study carried out before or after their smoking test. In 5 normal subjects, disappearance rates were determined before and during "sham" smoking of an unlit cigarette for 10 to 12 minutes. These subjects were instructed to "inhale" and "smoke" at their normal rate.

Six normal subjects (average age of 25 years) received 4 mg. of nicotine bitartrate intravenously while calf plethysmographic flows and NaI\textsuperscript{131} disappearance rates were measured. The nicotine bitartrate was diluted in 100 ml. of saline and administered by a constant-infusion pump over a 10- to 12-minute period via the tubing of an intravenous infusion which ran throughout the experiment.

Results

Normal Subjects and Smoking

The average NaI\textsuperscript{131} control clearance K of 0.053 increased by 24.5 per cent to a K of 0.066 during cigarette smoking in the 17 normal subjects (table 1). Fourteen of the 17 subjects showed an increased disappearance rate during smoking. The disappearance rate returned to control levels after smoking in 6 of the 14 positive tests while 8 continued to show an increased rate for the 5 to 10 minutes the counts were followed. However, plethysmographic calf blood flow changes varied. The average calf blood flow of 3.5 cc./100 cc. of tissue/minute decreased only 0.1 cc. during smoking. Table 1 also demonstrates that NaI\textsuperscript{131} disappearance rate and plethysmographic calf blood flow changes did not always correspond. The toe and calf skin temperatures decreased an average of 3.3 and 0.8 F, respectively, although one subject showed no change in toe, and 2, no change in calf temperature. An average increase of 12 beats per minute occurred in pulse rate and of 9 mm. Hg in both systolic and diastolic blood pressure.

Table 1

<table>
<thead>
<tr>
<th>Clearance constants</th>
<th>Calf blood flow*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Smoking</td>
<td>Control Smoking</td>
</tr>
<tr>
<td>0.073 0.100</td>
<td>1.8 1.6</td>
</tr>
<tr>
<td>0.078 0.103</td>
<td>3.2 4.4</td>
</tr>
<tr>
<td>0.051 0.073</td>
<td>3.5 2.4</td>
</tr>
<tr>
<td>0.067 0.067</td>
<td>4.2 3.8</td>
</tr>
<tr>
<td>0.045 0.059</td>
<td>2.3 2.3</td>
</tr>
<tr>
<td>0.064 0.074</td>
<td>3.6 3.0</td>
</tr>
<tr>
<td>0.066 0.103</td>
<td>5.0 3.8</td>
</tr>
<tr>
<td>0.030 0.047</td>
<td>4.3 3.9</td>
</tr>
<tr>
<td>0.062 0.062</td>
<td>2.7 2.8</td>
</tr>
<tr>
<td>0.028 0.032</td>
<td>3.1 2.8</td>
</tr>
<tr>
<td>0.018 0.022</td>
<td>5.4 5.1</td>
</tr>
<tr>
<td>0.042 0.042</td>
<td>2.1 2.2</td>
</tr>
<tr>
<td>0.029 0.038</td>
<td>4.9 5.5</td>
</tr>
<tr>
<td>0.048 0.066</td>
<td>†</td>
</tr>
<tr>
<td>0.045 0.052</td>
<td>†</td>
</tr>
<tr>
<td>0.071 0.082</td>
<td>†</td>
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<tr>
<td>0.080 0.094</td>
<td>†</td>
</tr>
<tr>
<td>Average 0.053 0.066</td>
<td>3.5 3.4</td>
</tr>
<tr>
<td>S.E. 0.0027</td>
<td>0.173</td>
</tr>
<tr>
<td>P     &lt;0.001</td>
<td>&lt;0.3</td>
</tr>
</tbody>
</table>

*cc./100 cc. of tissue/minute.
†Plethysmographic blood flow not measured.

Figure 1 illustrates the data from one experiment. The control disappearance rate with a K of 0.066 increased in about 1 minute after the subject started smoking to a K of 0.103. Following the end of smoking, the disappearance rate returned to parallel the control curve within 5 minutes. This subject showed a decrease in plethysmographic calf blood flow of about 0.8 cc./100 cc. of tissue/minute. The toe temperature decreased while the blood pressure and pulse rate rose.

NaI\textsuperscript{131} disappearance curves were performed on 8 of the subjects without smoking during a separate study carried out either before or after their smoking test. Each of
Nicotine Bitartrate Intravenous

depicts the data from one of the intravenous nicotine experiments. The control NaI\(^{131}\) disappearance rate with a K of 0.031 increased to 0.041 about 3 minutes after the infusion began. Following the infusion, the disappearance rate slowed. Plethysmographic calf blood flow increased 1.4 cc./100 cc. of tissue/minute.

"Sham" Smoking

In 5 subjects, disappearance rates were determined before and during "sham" smoking of an unlit cigarette. The control clearance constant K was 0.048 and did not change during "sham" smoking; each of the disappearance rates plotted as a straight line.

these control disappearance curves plotted as a straight line whereas 7 of these 8 subjects demonstrated an increase in disappearance rate during the smoking test.

Four subjects, who demonstrated an increased disappearance rate of NaI\(^{131}\) during cigarette smoking, were retested at another time. Each reacted in a similar manner during the repeat test. Their control clearance constant K of 0.057 increased to a K of 0.072 during smoking (S.E. = 0.002, \(p < 0.05\)). Average systolic and diastolic blood pressure rose 12 and 17 mm. Hg, respectively; pulse rate rose 18 beats per minute. Average toe and calf skin temperature decreased 3.5 and 1.6 F, respectively. All subjects experienced aching in the arm into which nicotine was infused. One subject, the only nonsmoker of the group, developed nausea and vomiting.

Figure 2 depicts the data from one of the intravenous nicotine experiments. The control NaI\(^{131}\) disappearance rate with a K of 0.031 increased to 0.041 about 3 minutes after the infusion began. Following the infusion, the disappearance rate slowed. Plethysmographic calf blood flow increased 1.4 cc./100 cc. of tissue/minute.

The effect of cigarette smoking on NaI\(^{131}\) disappearance rate from calf muscle and on plethysmographic calf blood flow.

In 5 experiments, the plethysmographic calf blood flow increased while one showed a decrease. Total calf blood flow increased from an average control level of 3.8 cc. to 4.5 cc./100 cc. of tissue/minute during the nicotine infusion (S.E. = 0.0703, \(p < 0.05\)). Average systolic and diastolic blood pressure rose 12 and 17 mm. Hg, respectively; pulse rate rose 18 beats per minute. Average toe and calf skin temperature decreased 3.5 and 1.6 F, respectively. All subjects experienced aching in the arm into which nicotine was infused. One subject, the only nonsmoker of the group, developed nausea and vomiting.

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Four of the 5 subjects who demonstrated a straight disappearance curve during "sham" smoking showed an increased disappearance rate during actual smoking. Blood pressure showed inconsistent changes and pulse rate rose in one subject during "sham" smoking while plethysmographic calf blood flow and toe skin temperature decreased an average of 1.0 cc./100 cc. of tissue/minute and 2.1 F., respectively. The upper curve of figure 3 depicts a "sham" smoking test. The disappearance rate is a straight line and is therefore unaffected by the period of "sham" smoking. The disappearance curve of the lower half of figure 3 is a real smoking test by the same subject and shows a more rapid disappearance rate during actual smoking.

Lumbar sympathectomies

NaI$^{131}$ disappearance rates were studied in 4 patients with lumbar sympathectomies performed for vasomotor disorders or arteriosclerosis obliterans. Plethysmographic blood flows were not measured. The average control clearance constant $K$ for these 4 patients of 0.033 increased to 0.047 during smoking (S.E. = 0.0078, $p < 0.2$). Three of the 4 subjects demonstrated an increased disappearance rate during smoking. Blood pressure and pulse rate rose in 3 of the 4 patients. Toe and calf skin temperatures did not decrease except in the one patient whose disappearance rate did not increase during smoking.

Arteriosclerosis obliterans

Six patients with bilateral arteriosclerosis obliterans of the lower extremities had straight NaI$^{131}$ disappearance curves during cigarette smoking. The average control $K$ of 0.035 did not change. Plethysmographic calf blood flows showed small decreases or increases but averaged 3.5 cc./100 cc. of tissue/minute before and during smoking (S.E. = 0.1414, $p > 0.5$). Blood pressures and pulse rates increased while skin temperature changes were small and variable.

Discussion

Of a group of 17 normal subjects, 14 showed an increase in skeletal muscle capillary blood flow as measured by the radioisotope disappearance rate during smoking despite insignificant changes in total calf blood flow and the usual decreases in skin temperature. Substantiation of these findings is found in a study by Ruef et al.,$^9$ who demonstrated a moderate increase in muscle blood flow during smoking, using a thermoelectric needle as a flow indicator. Also, Rottenstein and his group$^{10}$ have reported that 0.4 to 3.0 mg. of nicotine given intravenously increases the plethysmographic calf blood flow when the skin blood flow has been stopped by iontophoresis with adrenalin. They also showed some increase in plethysmographic calf blood flow with cigarette smoking in 5 of 8 tests on 6 subjects.

The repeat studies on subjects who had a more rapid disappearance rate during smoking revealed the constancy of the increase in blood flow while the "sham" smoking tests...
indicate that inhalation is not a factor. Also intravenous nicotine, in doses comparable to the amount contained in cigarettes, was shown by both the radioisotope and plethysmographic technics to be capable of increasing muscle blood flow significantly. Evidently the response is not dependent on an intact sympathetic nervous supply, for in 3 of 4 sympathectomized limbs there was an increased disappearance rate during smoking.

The mechanism of the increase in muscle blood flow during cigarette smoking or intravenous nicotine is uncertain. Hilton demonstrated that increases in gastrocnemius muscle blood flow in the cat from small doses of intra-arterial nicotine could be attributed to an axon reflex in cholinergic vasodilator fibers and also to a direct action of nicotine on muscle blood vessels. Irving and Yamamoto found that cigarette smoking or intravenous nicotine increased cardiac output and stroke volume in habitual smokers. Since a few of our subjects had positive tests with minimal or no change in blood pressure, it is difficult to explain the increased muscle blood flow entirely on the basis of an increased cardiac output. Stimulation of the adrenal medulla with a rise in circulating epinephrine levels occurs with nicotine; the muscle vasodilating properties of epinephrine could play a role. It would appear that a direct action of nicotine, an axon reflex, an increased cardiac output, and the vasodilating effect of epinephrine may all take part in increasing muscle blood flow during smoking.

In the 6 patients with arteriosclerosis obliterans no change in muscle capillary blood flow was found during cigarette smoking. This probably indicates the nonreactivity of the diseased vessels. Since capillary blood flow did not decrease, smoking evidently would not aggravate the symptom, intermittent claudication. This view has been expressed by others from clinical observations. However, though skeletal muscle blood flow may increase during cigarette smoking, skin flow definitely decreases and this is the factor of most importance to the patient with peripheral vascular disease. Such patients often are able to adjust to their intermittent claudication but their morbidity and mortality result from a decreased skin blood flow leading to rest pain and gangrene. Therefore it is still of importance to recommend that patients with ischemic peripheral vascular disease stop smoking.

Summary

Blood flow in the human calf during cigarette smoking was measured by two methods. One technic, the disappearance rate of a radioisotope injected into a muscle, was used to indicate muscle capillary blood flow, while the other method, plethysmography, was used to measure the total blood flow of the calf including both skin and muscle. The smoking of 2 unfiltered, regular-size cigarettes produced a significant increase in muscle capillary blood flow in 14 of 17 normal subjects while plethysmographic blood flow changes were variable and not significant. Tests were performed to demonstrate that the increased muscle blood flow was not secondary to inhalation, that it was reproducible, and that the sympathetic nervous system probably was not involved. Intravenous nicotine produced significant increases in both muscle capillary and total calf blood flow. Patients with arteriosclerosis obliterans showed no change in muscle capillary blood flow during smoking.

References


Anatomical Observation
Anatomy is an indispensable step to the more complex science of physiology which explains the vital forces of the body and this, though it may be helped by anatomy, demands observation of or experiment on the living organism. Fabricius' description of the valves in the vein stimulated Harvey to find out their use by the experimental method. Gaskell's physiological demonstration of the muscular continuity between the auricle and the ventricle was made on reptiles and was supposed to be confined to them until 1893, when the auriculo-ventricular bundle was described in mammals by Stanley Kent and by W. His, junior; in 1906 Tawara gave a full account of the junctional system, including the auriculo-ventricular node and the bundle previously described by Kent and His, the fibres of the bundle being combined into the Purkinje fibres which line the interior of the ventricles and communicate with their muscular fibres; this was followed in 1907 by Keith and Flack's discovery of the sino-auricular node, the normal pacemaker of the mammalian heart; the later anatomical observations were subsequent to and directly stimulated by the needs of the new cardiology, for Mackenzie's epoch-making book on the pulse was published in 1902.—SIR HUMPHRY DAVY ROLLESTON. The Harveian Oration. Great Britain, Cambridge University Press, 1928, p. 6.
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