IMPAIRED MICROVASCULAR VASODILATOR RESERVE
IN CHRONIC CIGARETTE SMOKERS
— A Study of Post-occlusive Reactive Hyperemia
in the Human Finger —

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To assess the vasodilator reserve in microcirculation, post-occlusive reactive hyperemia was examined in 21 chronic cigarette smokers (mean age: 50 ± 7 years) and 21 non-smokers (mean age: 51 ± 6 years), who were all healthy males. Reactive hyperemia was induced by occluding the digital artery at the base of the middle finger, and the increase in skin blood flow (Δ flow) was analyzed with a laser Doppler flowmeter. Occlusion time was increased in a stepwise manner from 30 sec up to 300 sec. Baseline skin blood flow was similar in both groups (smoker, 27 ± 9 ml/min/100 g; non-smoker, 25 ± 10 ml/min/100 g, NS). The Δ flow in smokers was significantly less (23%–59%) than that in non-smokers. Furthermore, the reduced Δ flow in smokers was inversely correlated with Brinkmann’s smoking index (r = 0.567, p < 0.01). These results indicate that chronic cigarette smoking impairs the microvascular response to transient ischemia, and that this impairment correlates with the intensity of the smoking habit.

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Cigarette smoking is an established risk factor for coronary heart disease as well as for peripheral vascular disease!—3 Recent study has shown that smoking is also a risk factor for stroke!—5 Taken together, smoking has generalized adverse effects on the cardiovascular system. However, due to methodological problems, less clinical work has been directed toward the changes that occur in the microcirculatory system of smokers. Because of its simplicity, the recent introduction of the laser Doppler flowmeter has facilitated the clinical investigation of microvascular behavior in response to various stimuli. This apparatus also makes it possible to continuously monitor the microvascular flow velocity.

According to the Framingham study! males are nearly twice as susceptible to coronary heart disease as females. Moreover, males are also more susceptible to peripheral vascular disease than females? These facts led me to investigate the microvascular response to transient ischemia in male 40- to 60-year-old cigarette smokers utilizing a laser Doppler flowmeter.

METHODS

Laser Doppler Flowmetry
A laser Doppler flowmeter (ALF-2100, Advance Co, Ltd, Tokyo) was used to continuously monitor cutaneous blood flow at the distal phalanx of the middle finger. Flow

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changes were recorded on a Unicorder U-228 (Nippon Denshi Kagaku Co, Ltd, Kyoto) at a chart speed of 30 mm/min. The basic theory of laser Doppler flowmetry has been described elsewhere. This device consists of a helium-neon laser, an electronic circuit, and a pair of fiber-optic light guides which carry the laser beam to and from a given tissue to a photodetector. The 2 fiber-optic guides are separated by a distance of 0.6 mm. The laser beam penetrates tissue to a depth of approximately 1 mm in a hemispherical fashion. Moving red cells in a capillary produce a Doppler shift in the reflected light and its frequency is converted to a Doppler shifted signal which is linearly correlated with microcirculatory blood flow. This apparatus was calibrated by perfusion experiments using a canine intestine preparation which was constantly perfused at known perfusion rates.

Subjects and Experimental Design
The subjects of this study consisted of 42 middle-aged men: 21 chronic cigarette smokers and 21 age-matched non-smokers. The smokers were all inhalers. The mean age (±SD) of the smokers was 50±7 years (range 40 to 59 years) and that of the non-smokers was 51±6 years (range 41 to 60 years; NS). All of the subjects were healthy volunteers with normal blood pressures: systolic blood pressure below 140 mmHg and diastolic blood pressure below 90 mmHg. None of the subjects had a history of cardiovascular disease. Moreover, none of the subjects were receiving medications, including non-steroidal anti-inflammatory drugs which inhibit the biosynthesis of prostaglandins and which have been shown to affect reactive hyperemia prior to the study. The cigarette smokers refrained from smoking for at least 2 h prior to the study. All of the experiments were performed in the morning in a quiet air-conditioned room. Room temperature was adjusted to 25–26 °C. After 30 min of resting in a supine position, systolic and diastolic blood pressure and heart rate were measured. Arterial occlusion was performed by inflating a cuff placed around the base of the middle finger to a pressure of 50–60 mmHg above the subject’s systolic blood pressure. The occlusion time was increased in a stepwise manner from 30 sec to 60, 120, 180, 240 and 300 sec for each subject. Recordings of hyperemic responses were separated by a sufficient recovery time of at least 5 min to stabilize the microvascular tone before the next occlusion was begun: in a preliminary study (n=6), the hyperemic response with 300 sec of occlusion was highly reproducible when 5 min intervals were used (Δflow: 24±6 vs 23±5 ml/min/100 g, NS; T1/2: 42±26 vs 44±29 sec, NS). The entire experiment lasted approximately 90 min per subject.

TABLE I  BASELINE CHARACTERISTICS OF THE STUDY POPULATION

<table>
<thead>
<tr>
<th>Variables</th>
<th>Smokers</th>
<th>Non-smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168±5</td>
<td>167±5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66±7</td>
<td>66±7</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>24±3</td>
<td>24±2</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>123±7</td>
<td>126±10</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>78±5</td>
<td>80±6</td>
</tr>
<tr>
<td>Heart Rate (beats/min)</td>
<td>70±7</td>
<td>70±10</td>
</tr>
<tr>
<td>Skin Surface Temperature</td>
<td>34.5±0.7</td>
<td>34.7±0.6</td>
</tr>
</tbody>
</table>

Fig.2. Scatterplot of baseline skin blood flow in smokers and nonsmokers.

Baseline skin blood flow was determined by averaging 10 readings that were taken every 12 sec before occlusion. The Δflow was determined as indicated in Fig. 1. T1/2 was defined as the length of the period from the release of occlusion to the point at which peak blood flow was reduced by 50%. Skin surface temperature was measured before and after the experiment with an ordinary thermometer (Shibaura Electronics Co, Ltd, Tokyo), and was averaged to show the condition of the experiment.

All data are presented as the mean±SD. To determine whether the Δflow was significantly affected by occlusion time, the data were analyzed by a repeated-measures one-way analysis of variance (ANOVA). When a significant difference was found, Scheffe’s test was used to determine the significance between groups. A two-tailed Student’s t test was used to compare baseline characteristics. The relation between Δflow and occlusion time was evaluated by using Spear-

Fig.3. Bar graph showing the Δflow in smokers and non-smokers. Error bars represent standard deviations.

TABLE II  HALF TIME FOR RECOVERY (T1/2) IN SMOKERS AND NON-SMOKERS

<table>
<thead>
<tr>
<th>Occlusion time</th>
<th>Smokers</th>
<th>Non-smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 sec</td>
<td>5±5</td>
<td>7±4</td>
</tr>
<tr>
<td>60 sec</td>
<td>10±8</td>
<td>13±12</td>
</tr>
<tr>
<td>120 sec</td>
<td>16±11</td>
<td>14±9</td>
</tr>
<tr>
<td>180 sec</td>
<td>21±19</td>
<td>20±14</td>
</tr>
<tr>
<td>240 sec</td>
<td>26±23</td>
<td>31±17</td>
</tr>
<tr>
<td>300 sec</td>
<td>37±29</td>
<td>43±46</td>
</tr>
</tbody>
</table>

Values are indicated in seconds as mean±SD.

man’s correlation coefficient. A p value of less than 0.05 was considered statistically significant.

RESULTS

There were no significant differences between the baseline characteristics of smokers and non-smokers (Table I).

Baseline skin blood flow was 27±9 ml/min/100 g for smokers and 25±10 ml/min/100 g for non-smokers (Fig. 2, NS). The Δflow proportionally increased in both groups as the occlusion time was increased from 30 sec up to 300 sec. However, the cigarette smokers always showed a lower Δflow (p<0.01) than the non-smokers (Fig. 3). The value of Δflow in smokers was from 23% to 59% of that in non-smokers. The T1/2 for recovery tended to be longer in non-smokers than in smokers at 240 sec and 300 sec of occlusion (0.1>p>0.05, Table II).

To assess the relationship between smok-
ing history and a reduced reactive hyperemic response. Brinkmann’s smoking index was plotted against the Δflow following 300 sec of occlusion (Fig. 4). This plot showed a significant inverse correlation ($r = -0.567$, $p < 0.01$), indicating that the reduced reactive hyperemic response in smokers is related to the intensity of the smoking habit.

**DISCUSSION**

This study in middle-aged men demonstrates that the microvascular response against transient ischemia is markedly reduced in habitual smokers. This finding agrees with established studies by Carlsson and Wennmalm$^{11}$ who used venous occlusion plethysmography, and by Richardson$^{12}$ who studied female subjects using a Doppler velocity meter at the radial artery. The present study has further extended the evidence that the reduced reactive hyperemic response is closely related to the intensity of the smoking habit (Fig. 4).

Although the mechanism involved in the inhibitory effect of cigarette smoking on the reactive hyperemic response is not fully established, it is known that prostaglandine plays a role.$^{9,13}$ Myogenic and metabolic factors, which interact closely with each other, are thought to regulate the intensity of reactive hyperemia. On the other hand, the autonomic nervous system is not likely to be involved in this response.$^{13}$ The myogenic factor, or Bayliss mechanism,$^{14}$ may play a major role in post-occlusive reactive hyperemia, as stressed by Folkow.$^{15}$ The metabolic factors include hypoxic vasodilation, accumulation of vasodilator metabolites produced or released during ischemia, and depletion of key substrates due to the circulatory arrest. Vascular prostaglandin is known to be one of the metabolic factors which are involved in reactive hyperemia because inhibition of the cyclooxygenase pathway with non-steroidal anti-inflammatory agents causes a reduction of the hyperemic response in non-smokers,$^{16}$ but not in smokers.$^{11}$ Adenosine, a potent vasodilator, is also known to play an important role because theophylline, an adenosine receptor antagonist, reduces reactive hyperemia. Moreover, it has been shown that dipyrimate, which inhibits the degradation of adenosine, potentiates reactive hyperemia in non-smokers.$^{16}$ However, the effects of these drugs have not been studied in smokers.

Another possible explanation for the reduced reactive hyperemia in smokers is increased platelet aggregability due to the enhanced production of thromboxane A2.$^{17}$ If more platelets aggregate during the brief

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period of ischemia, flow recovery may be disturbed by obstruction of the microvasculature. Neutrophils and macrophages may also play an important role in this regard, especially at the postcapillary venule.18

Because different tissues and organs have their own metabolic regulation, their mechanisms of reactive hyperemia are likely to be different. Thus, the present results are specific for cutaneous reactive hyperemia and cannot be applied to other tissues and organs. However, if vasodilating capacity following a brief period of ischemia is reduced in coronary circulation among smokers, then recovery from vasospasm may be impaired in patients with vasospastic angina who smoke cigarettes. Similarly, if such is the case in cerebral circulation, then recovery from vasospasm, which frequently occurs following subarachnoidal hemorrhage, may also be impaired among smokers. These proposed mechanisms may be related to the high rate of mortality due to coronary heart disease and stroke among smokers1,4,5 These hypotheses should be investigated in the future.

In conclusion, chronic cigarette smoking attenuates the microvascular vasodilator reserve against transient ischemia in middle-aged men who have no clinically overt cardiovascular disease. This impairment is related to the intensity of the smoking habit. The precise mechanisms underlying this phenomenon should be elucidated in a future study.

REFERENCES


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