Effects of Smoking on Regional Cerebral Blood Flow in Neurologically Normal Subjects

KAZUO KUBOTA, M.D., PH.D., TATSUO YAMAGUCHI, M.D., YOSHINAO ABE, M.D., TAKEHIKO FUJIWARA, M.D., JUN HATAZAWA, M.D., PH.D., AND TAIJU MATSUZAWA, M.D., PH.D.

SUMMARY The chronic effects of smoking on regional cerebral blood flow (CBF), and on serum lipids and lipoprotein levels in neurologically normal subjects, were studied. CBF was studied by the 133-Xenon inhalation method and gray matter flow was calculated following the method of Obrist et al. One hundred and eleven subjects, who had no abnormalities in neurological examinations nor in CT scans, were divided into two groups: smokers (37) and non-smokers (74). Those who had a smoking index (Number of cigarettes/day) x (years of smoking history) > 200 were designated as smokers. The mean smoking index of smokers was 760. Sixty-two of the 74 subjects in the non-smoking group had never smoked, and the mean smoking index of non-smokers was 17. In the male, CBF was significantly lower in smokers than in non-smokers (mean CBF, 12.5% lower in smokers, p < 0.001). Increased reduction of CBF with advancing age was also observed. Compared to non-smokers, CBF in smokers was found to be significantly lower than the expected age matched value. Serum high density lipoprotein cholesterol values in smokers were significantly lower, and total cholesterol levels significantly higher than in non-smokers. We concluded that smoking chronically reduces CBF. Decrease of CBF in smokers was probably due to advanced atherosclerosis which produces vascular narrowing and raised resistance in cerebral blood vessels.

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significant difference of CBF value between non-smokers and light smokers. The mean age of both groups, smoking and non-smoking, were identical.

All 111 patients had visited the outpatient clinic. Their clinical presentations were as follows; 74 non-smokers: vertigo 23, headache 16, transient ischaemic attacks (TIA) 16, volunteer 5, hypertension 8, diabetes mellitus (DM) 5, and others 3. 37 smokers: vertigo 11, headache 8, TIA 10, hypertension 4, DM 1, and others 2, but no abnormality in CT scan, nor any neurological signs were observed during examinations.

Each patient had a detailed history and complete cardiovascular and neurological examinations including CT scan, pulmonary function tests, chest X-rays, and physical examination. Subjects with pulmonary dysfunctions were excluded. Informed consent of subjects was obtained for all CBF studies. Patients with subarachnoidal hemorrhage, brain tumor, head trauma, chronic subdural hematoma, mental impairment and previous history of CVD were also excluded.

**Results**

Figure 1 shows the distribution of smoking indices for all subjects. The purpose of this study is to observe the chronic effect of smoking on the CBF. We separate the subjects into three groups according to their smoking indices; 0, from 1 to 200, and more than 200.

Table 1 presents the distribution of Subjects and CBF Values (ml/100 g brain tissue/min).

<table>
<thead>
<tr>
<th>Smoking index (mean ± SD)</th>
<th>n</th>
<th>left hemisphere</th>
<th>CBF (ml/100 g/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>62(F52, M10)</td>
<td>73.3 ± 9.3</td>
<td>56.7 ± 12.8</td>
</tr>
<tr>
<td>1 ~ 200</td>
<td>12(F6, M6)</td>
<td>75.8 ± 6.3</td>
<td>51.4 ± 17.4</td>
</tr>
<tr>
<td>200 &lt;</td>
<td>37(F2, M35)</td>
<td>64.5 ± 12.0</td>
<td>56.0 ± 12.7</td>
</tr>
</tbody>
</table>

Smoking index: (number of cigarettes/day) \times (years of smoking history).

CBF in smokers was lower than the expected age-matched value of non-smokers.

Mean hemispheric CBF values are compared in Table 1. Mean CBF was significantly lower in smokers (12.5%, $p < 0.001$) compared to non-smokers in both right and left hemispheres.

Figure 3 shows CBF values of the individual detectors for the smokers and non-smokers. CBF values for the smokers were significantly and equally low in all hemispheres.

**Figure 1.** Distribution of smoking indices for all subjects. Smoking Index: (Number of cigarettes/day) \times (years of smoking history)

**Figure 2.** Mean brain CBF values plotted against age of subjects. The regression line of non-smokers fitted by the least square method shows the age-dependent decrease of CBF. Non-smokers are represented as open symbols (o). Smokers represented as closed symbols (•) have lower CBF values than non-smokers and also showed age-dependent decrease.

Y = -0.305 X + 92.4 $r = 0.487$ $n = 74$ $p < 0.001$

for non-smokers.

Y = -0.276 X + 80.5 $r = 0.326$ $n = 37$ $p < 0.05$

for smokers.
FIGURE 3. Individual detector positions against left hemisphere (channel 1 to 7) and right hemisphere (channel 8 to 14). CBF value of each detector in the 74 non-smokers (white column) was compared with those of the 37 smokers (darkened column). The results of Student's t-test were as follows: Ch 3-5, 7, 9, 11, 13: p < 0.001, Ch 8, 10, 14: p < 0.002, Ch 6: p < 0.005, Ch 2, 12: p < 0.01, Ch 1: p < 0.05.

detectors compared to those of non-smokers. CBF values for both groups were significantly higher in the anterior than in the posterior regions for both hemispheres. With the smoking and non-smoking groups, there were no significant differences in the mean hemispheric and in individual CBF values obtained from parallel regions between the right and left hemispheres.

Serum lipid and lipoprotein levels were also determined in all the subjects (table 2). The mean HDL-cholesterol value in male smokers was significantly lower than in non-smoking males. And total cholesterol levels in male smokers was significantly higher than in male non-smokers. In the non-smoking group, both total cholesterol and triglyceride levels were higher in females than in males. Table 2 shows that there were no significant differences in CBF values between males and females in the non-smoking group, but only significant differences between smokers and non-smokers in the male.

Discussion

The acute effects of smoking have already been described to either increase\(^5,6\) or have no effect on CBF.\(^4\) In these studies increased CBF was probably the pharmacological effect of nicotine and other cigarette compounds and their results conflicted with the accepted notion that cigarettes are a risk factor for atherosclerosis and CVD. We therefore suspected that the acute pharmacological effects and accumulating chronic effects of smoking on CBF were probably quite different. CBF in smokers was significantly lower than in non-smokers in this study. Smokers whose mean smoking index was 760, were recognized as long term or chronic smokers, and were prohibited to smoke for 3 hours before the examination. Three hours are considered to be enough to eliminate the acute effect of smoking on cardiovascular system.\(^10,11\) Consequently the chronic rather than the acute effect of smoking were observed in this study. Our findings are compatible with the results of epidemiological studies, and clearly show that the chronic opposed to the acute effects of smoking are more harmful to the brain. Because of the limited number of subjects, we could not show the dose-response curve between the smoking index and CBF value in this study.

Since our subjects included volunteers as well as patients who visited the hospital and proved neurologically normal, the standard deviation of CBF in them was rather large. This fact, however did not affect our results. Hypertension and diabetes patients were included, but they comprised only about 10 percent of each of the smoking and non-smoking groups. The age distribution of the subjects were identical between the smoking and non-smoking groups. No significant differences in CBF were observed between males and females in the non-smoking group. Since there are only two smoker females, we observed significant differences of CBF between smoker and non-smoker only in the male subjects.

It may be argued that in smokers, pulmonary changes occur which interfere with the exchange of Xenon between lung and blood, and distort the computed CBF values. However, this possibility is remote since subjects with clinical or roentgenographic or pulmonary functional evidence for pulmonary abnormalities were excluded from the present study. Therefore we concluded that the CBF reduction observed in smokers was essentially due to the chronic effects of smoking.

Reduction in CBF during normal aging has already been reported\(^12-23\) and we also observed a progressive reduction of CBF with advancing age in this study. This phenomenon is thought to be caused by reduced cerebral neurons,\(^24\) and diminished metabolism, or arteriosclerosis.\(^21\) Age-related brain atrophy which was recently studied quantitatively with computed tomography,\(^25,26\) gave roentgenographic support to the age-related reduction of CBF. Moreover we observed significantly advanced brain atrophy in smokers com-
pared to non-smokers in a preliminary study. All of these results strongly support our finding that smoking significantly reduces CBF.

In this study, HDL-cholesterol in smokers was significantly lower and total cholesterol higher than in non-smokers. This was consistent with previous reports in which low serum HDL-cholesterol and high total cholesterol were suggested to be important atherogenic factors. Many epidemiological studies have already described advanced atherosclerosis and atherosclerotic disease due to cigarette smoking, and others have reported lower CBF in subjects with risk factors for atherothrombotic stroke compared to normal subjects. Based on these and our present findings we proposed therefore that a clear correlation exists between smokers, low HDL-cholesterol and high total cholesterol, advanced atherosclerosis and reduced CBF. Decreased CBF in smokers is therefore a direct result of advanced atherosclerosis which produces vascular narrowing and raised resistance in cerebral blood vessels.

In this report, we are the first to show that chronic smoking reduces CBF in neurologically normal subjects. This decreased CBF observed in smokers cannot be accounted for by the pharmacological effects of cigarettes but is probably the result of advanced cerebral atherosclerosis. Since decreased CBF due to atherosclerosis will finally result in a high incidence of CVD in smokers, our study should clearly help people to stop smoking.

Acknowledgments
We would like to thank Mr. Shinya Itagaki, and Mr. Atushi Ohnai for their excellent technical assistance, and Dr. Yuichiro Sasaki for his excellent advice concerning the patients.

References


Table 2: Serum Total Cholesterol, Triglycerides, and HDL-Cholesterol in Smokers and Non-smokers (mg/dl), and CBF Values for Each

<table>
<thead>
<tr>
<th></th>
<th>Non-smoker</th>
<th>Smoker</th>
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<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>n</td>
<td>16</td>
<td>58</td>
</tr>
<tr>
<td>T. cholesterol (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>173.4±41.2</td>
<td>206.3±36.9*</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>103.3±46.4</td>
<td>149.7±63.7†</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>56.2±11.1</td>
<td>51.0±11.0</td>
</tr>
<tr>
<td>CBF (ml/100 g/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>left hemisphere</td>
<td>75.4±11.1</td>
<td>73.3±9.2</td>
</tr>
<tr>
<td>right hemisphere</td>
<td>76.8±11.3</td>
<td>73.8±9.3</td>
</tr>
</tbody>
</table>

* p < 0.05, differences from male non-smokers.
† p < 0.01, differences from male non-smokers.
‡ p < 0.001, differences from male non-smokers.
No Effect of Prostacyclin on Blood Flow, Regulation of Blood Flow and Blood Coagulation Following Global Cerebral Ischemia

W. VAN DEN KERCKHOFF, K.-A. HOSSMANN AND V. HOSSMANN*

SUMMARY  In normothermic cats under light barbiturate anesthesia, cerebral blood flow was arrested for one hour by intrathoracal occlusion of the innominate, the left subclavian, and both mammarian arteries. Recirculation of the brain after ischemia resulted in reactive hyperemia, followed by a decrease of blood flow to about 70% of control (post-ischemic hypoperfusion). During postischemic hypoperfusion, CO2-reactivity was completely abolished. Intravenous infusion of prostacyclin 2 hours after ischemia (1.8 μg/kg/min) decreased systemic arterial blood pressure and reduced platelet aggregability but did not improve cerebral blood flow, did not restore CO2-reactivity, and did not influence postischemic changes of blood coagulation. It is concluded that prostacyclin deficiency is not or not the only reason for the development of post-ischemic hypoperfusion and the associated disturbance of flow regulation.

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THROUGHOUT THE COURSE of reperfusion after a period of complete cerebro-circulatory arrest, certain physiological and metabolic phenomena develop in a regular sequence: the early reperfusion period is characterized by a shortlasting reactive hyperemia, followed by a phase of reduced blood circulation (post-ischemic hypoperfusion). During both phases, energy-producing metabolism and blood flow are uncoupled: in reactive hyperemia, oxygen availability exceeds the oxygen requirements of the tissue, and oxygen content of cerebral venous blood increases (luxury perfusion).1 During post-ischemic hypoperfusion, the decreased oxygen availability is in misrelationship to an increased metabolic demand of the tissue and therefore may result in relative cerebral hypoxia.2

The hemodynamic changes are caused by or associated with disturbances of flow regulation. During reactive hyperemia, cerebral vessels are paralyzed, and both CO2-reactivity and autoregulation are abolished. During subsequent post-ischemic hypoperfusion, in contrast, vascular tone is increased although CO2-reactivity is abolished, and a rise of blood pressure now causes an autoregulatory constriction of the resistance vessels. In consequence, blood flow in this period of hypoperfusion cannot be improved by either increasing blood pressure or increasing arterial or tissue pCO2.3

The hemodynamic changes observed during postischemic hypoperfusion resemble the pharmacological effect of indomethacin, an inhibitor of prostaglandin synthesis, which also reduces blood flow and abolishes CO2-reactivity without interfering with autoregulation.4 Prostaglandins have been shown to play an important role in the hemodynamic balance of local blood flow in microcirculation, whereby prostacyclin (PGI2) and thromboxane A2 (TXA2) are mainly involved. The respective precursors are the cyclic endoperoxides PGG2 and PGH2, that are synthetized from arachidonic acid by cyclo-oxygenases. These endoperoxides are transformed in the vascular wall by prostacyclin synthetase into PGI2,5-7 and in the blood platelets by thromboxane-synthetase into TXA2.8-11 PGI2 is the most potent physiological vasodilator known and a strong antiaggregatory compound. TXA2, on the other hand, is an effective platelet aggregator and a strong vasoconstrictor.8,10,12-14

Although both PGI2 and TXA2 synthesis are inhibited by indomethacin, the main factor responsible for the hemodynamic changes seems to be the reduced synthesis of PGI2, because substitution of this compound reverses the reduction of cerebral blood flow and restores
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