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

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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.

Methods

Regional cerebral blood flow was measured by the 133-Xenon inhalation method using the Aloka RRG-526 CBF measurement system (Aloka Co., Ltd., Tokyo). The study was carried out with patients lying on a bed with closed eyes covered with gauze in a quiet semidarkened room. Smoking was prohibited for them from three hours before examination. Radioactive Xenon gas inhalation procedures according to Obrist et al. were followed, where 1 minute of inhalation was followed by 10 minutes of clearance. Cerebral activity was monitored by 7 pairs of NaI(Tl) scintillation detectors, each 1 inch long and 1 inch in diameter held in parallel position on both sides of the subject's head. Endo-tidal air radioactivity was recorded by an additional detector and was used to correct the recirculation of Xenon gas. An arterial blood sample was drawn immediately after the test to determine pCO₂ and pO₂. Each detector was incorporated into an on-line computerized system. The CBF was computed according to Obrist et al., using a two compartmental model in which the faster clearing compartment was considered to represent the amount of blood flow in gray matter (Fₜ), and was expressed as ml per 100 g of brain tissue per minute.

Subjects

A hundred and eleven adult patients were studied by CT scan and CBF. The subjects consisted of 37 smokers and 74 non-smokers according to the smoking index described below. Those patients whose products of cigarettes smoked per day and years of smoking history were greater than two hundred [Smoking index (Number of cigarette/day) x (years of smoking history) > 200] were designated as smokers. The mean smoking index for smokers was 760. Our non-smoking group consisted of 62 subjects who had never smoked and 12 light smokers (mean smoking index 104). The mean smoking index of the 74 non-smokers was therefore 17. We disregarded the fact that the non-smoking group contained a mixed population since there was no...
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. There was no significant difference between the former two groups. Then, we set the discriminating level of smoking index for chronic smoker at 200.

Figure 2 presents the correlation between mean cerebral blood flow (CBF) (calculated for each subject from 14 bihemispheric CBF detector values) and age. There was a statistically significant reduction of CBF in both non-smoking and smoking groups with advancing age.

\[ Y = -0.305 X + 92.4 \quad r = 0.487 \quad n = 74 \quad p < 0.001 \]

for non-smokers.

\[ Y = -0.276 X + 80.5 \quad r = 0.326 \quad n = 37 \quad p < 0.05 \]

for smokers.

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 individuals.
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 cerebrovascular disease. 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. Atsushi Ohnai for their excellent technical assistance, and Dr. Yuichiro Sasaki for his excellent advice concerning the patients.

References
25. T. cholesterol (mg/dl) 173.4±41.2 206.3±36.9* 197.4±36.4* 227.5±9.2
26. Triglyceride (mg/dl) 103.3±46.4 149.7±63.7† 135.4±59.1 123.5±23.3
27. HDL-cholesterol (mg/dl) 56.2±11.1 51.0±11.0 47.7±13.6* 56.0±31.1
28. CBF (ml/100 g/min)

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Serum Total Cholesterol, Triglycerides, and HDL-Cholesterol in Smokers and Non-smokers (mg/dl), and CBF Values for Each</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
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<td>n</td>
<td>16</td>
<td>58</td>
<td>35</td>
<td>2</td>
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<tr>
<td>T. cholesterol (mg/dl)</td>
<td>173.4±41.2</td>
<td>206.3±36.9*</td>
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<td>227.5±9.2</td>
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<tr>
<td>Triglyceride (mg/dl)</td>
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<td>149.7±63.7†</td>
<td>135.4±59.1</td>
<td>123.5±23.3</td>
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<td>HDL-cholesterol (mg/dl)</td>
<td>56.2±11.1</td>
<td>51.0±11.0</td>
<td>47.7±13.6*</td>
<td>56.0±31.1</td>
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<tr>
<td>CBF (ml/100 g/min)</td>
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<tr>
<td>left hemisphere</td>
<td>75.4±11.1</td>
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<td>right hemisphere</td>
<td>76.8±11.3</td>
<td>73.8±9.3</td>
<td>64.3±12.1‡</td>
<td>81.0±4.2</td>
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</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.
During post-ischemic hypoperfusion, in both CO$_2$-reactivity and autoregulation are abolished.

Thromboxane A$_2$ (TXA$_2$) is the most potent physiological vasodilator known and a strong antiaggregatory compound. TXA$_2$, on the other hand, is an effective platelet aggregator and a strong vasoconstrictor.

Although both PGI$_2$ and TXA$_2$ synthesis are inhibited by indomethacin, the main factor responsible for the hemodynamic changes seems to be the reduced synthesis of PGI$_2$, because substitution of this compound reverses the reduction of cerebral blood flow and restores contrast, vascular tone is increased although CO$_2$-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 pCO$_2$.

The hemodynamic changes observed during post-ischemic hypoperfusion resemble the pharmacological effect of indomethacin, an inhibitor of prostaglandin synthesis, which also reduces blood flow and abolishes CO$_2$-reactivity without interfering with autoregulation. Prostaglandins have been shown to play an important role in the hemodynamic balance of local blood flow in microcirculation, whereby prostacyclin (PGI$_2$) and thromboxane A$_2$ (TXA$_2$) are mainly involved. The respective precursors are the cyclic endoperoxides PGG$_2$ and PGH$_2$, that are synthetized from arachidonic acid by cyclo-oxygenases. These endoperoxides are transformed in the vascular wall by prostacyclin thromboxane synthetase into TXA$_2$ and thromboxane synthetase into TXA$_2$. PGI$_2$ is the most potent physiological vasodilator known and a strong antiaggregatory compound.
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