Smoking and Fibrinolysis

By Lars Janzon, M.D., and Inga Marie Nilsson, M.D.

SUMMARY
In order to study the fibrinolytic activity of vein walls in smokers and nonsmokers, 71 randomly selected heavy smokers, i.e., smoking more than 15 g tobacco per day, and 41 nonsmokers from the population group "Men born in 1914 residing in Malmö" were invited to undergo a health examination. When examined after 12 hours' abstention from tobacco, the smokers were found to have the same fibrinolytic activity as nonsmokers. Out of the 71 heavy smokers, 31 refrained from smoking during 8–9 weeks (as monitored with questionnaire and COHb-determinations). Neither in those who had abstained from smoking nor in the controls did the fibrinolytic activity differ from that initially recorded. In a randomly selected subsample of 19 individuals examined after only one week's abstention from tobacco, the fibrinolytic activity, after venous occlusion of forearms, tended to be lower in the blood as well as in superficial hand veins, but the difference was not significant. The effect of smoking six cigarettes during three hours was measured. This level of smoking was associated with an increased fibrinolytic activity in blood, measured as euglobulin clot lysis time, and in superficial hand veins. This increase is probably due to the combined effects of nicotine and carbon monoxide.

Additional Indexing Words:
Plasminogen activators
Cigarettes

SPOONTANEOUS FIBRINOLYTIC ACTIVITY has been found to be lower in smokers than in nonsmokers, studied with Fearnley's method. The ages of the participants in these studies varied however, and it is not clear whether the patients were examined under basal conditions. It is now regarded as established that activators of fibrinolysis are formed in and released from the endothelium of small vessels. Venous occlusion causes a clear increase in the fibrinolytic activity in the occluded vessels caused by activators released from the vessel walls. Pandolfi's modification of Todd's histochemical method has now made it possible to estimate the level of activators of fibrinolysis present in superficial veins.

The aim of the present investigation was to study the effect of smoking and smoking cessation on the fibrinolytic activity of vessel walls with the above mentioned methods.

Clinical Procedure
From the population group "Men born in 1914 residing in Malmö" who took part in a mass health examination in 1969 and who were classified according to smoking habits, 105 of the heavy smokers (smoking more than 15 g tobacco per day) and 55 nonsmokers were randomly selected and invited to take part in the present investigation. Eighty-eight of the smokers and 41 of the nonsmokers cooperated. Of the smokers, 17 had stopped smoking since 1969 and were excluded from the investigation. Of the remaining 71, 58 were randomly selected and requested to stop smoking. Seven declined. These seven, together with 13 primarily randomly selected and 17 who failed to abstain from smoking, served as a control group. At the follow-up examination after 8–9 weeks, all of those 34 who had quit smoking were re-examined. Eight subjects in the control group did not come to the follow-up examination and only 29 individuals of the control group were therefore re-examined. Smoking abstinence was monitored by questionnaire and determination of carbon monoxide hemoglobin. The participants were always examined in the fasting state in the morning and before they had smoked.

A subsample consisting of 19 participants from those who quit smoking was examined after they had abstained from smoking for one week. The following variables were determined: 1) fibrinolytic activity after venous occlusion of the arms; 2) fibrinolytic activator activity in superficial hand veins; 3) carbon monoxide hemoglobin.

To assess the immediate effect of smoking, another 20 heavy smokers were randomly selected from the study group "Men born in 1914 residing in Malmö" and invited to take part in the investigation. Nineteen accepted. Ten were randomly allocated to examinations after having smoked six cigarettes during three hours and the other nine to examinations without having smoked. After 10–14 days they were re-examined after substituting the alternate protocol in each group. The following variables were determined: 1) platelet count; 2) platelet adhesiveness; 3) APTT (activated partial thromboplastin time); 4) AHF (factor VIII); 5) fibrinogen; 6) euglobulin clot lysis time; 7) fibrin/fibrinogen degradation products (FDP); 8) fibrinolytic activity in forearms after venous occlusion; 9) fibrinolytic activator ac-

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activity in superficial hand veins, and 10) carbon monoxide hemoglobin (COHb).

Methods
The following laboratory methods were used to measure the variables:

1) Platelet count: according to Björkman.
2) Platelet adhesiveness: according to Hellem.
3) APTT was measured according to the method described by Nilsson as the kaolin-cephalin-time with kaolin-cephalin-reagent (APTT, General Diagnostics).
4) AHF was determined by the method described by Nilsson et al.
5) Fibrinogen was measured with the method of Nilsson and Olow.
6) Fibrin/fibrinogen degradation products (FDP) were assessed with samples collected with addition of EACA were used.
7) Euglobulin clot lysis time. The method of Nilsson and Olow was used.
8) Fibrinolytic activity in the forearms following venous occlusion, determined on resuspended euglobulin precipitate on unheated fibrin plates. Venous occlusion was applied for 20 minutes with the aid of blood pressure cuffs wrapped around the forearms and inflated to a pressure intermediate systolic and diastolic pressure. Blood samples for measuring fibrinolytic activity in resuspended euglobulin precipitate were obtained from both arms just before deflation of the cuff. Normal range 158 to 500 mm².  
9) Fibrinolytic activator activity in the vein wall. The venous biopsy, about 1 cm long, was obtained under local anesthesia from a dorsal vein of the hand. The activity was then determined with Pandolfi's modification of Todd's histochemical method and the content of fibrinolytic activators was expressed in arbitrary units. The normal range for the forearm is 6 to 11 units.
10) COHb was determined with the method of Collison et al. Mean value + 1 sd (1%) of nonsmokers was used as a criterion for abstinence of smoking.

The significance of differences was tested with Student's two-tailed t-test. A P value smaller than 0.05 was regarded as statistically significant.

Table 1
Comparison of Fibrinolytic Activity in Smokers and Nonsmokers*

<table>
<thead>
<tr>
<th></th>
<th>After VO†</th>
<th>In SV†</th>
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<tbody>
<tr>
<td>Nonsmokers</td>
<td></td>
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<tr>
<td>N = 40</td>
<td>255 ± 22</td>
<td>6.7 ± 0.2</td>
</tr>
<tr>
<td>N = 71</td>
<td>229 ± 16</td>
<td>6.5 ± 0.2</td>
</tr>
<tr>
<td>Smokers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Values are mean ± standard error.
†Fibrinolytic activity after venous occlusion (VO) (lysed area in mm²).
‡Fibrinolytic activity in superficial veins (SV) (arbitrary units).
NS = not significant.

Results
Comparison between Fibrinolytic Activity in Smokers and Nonsmokers

The results are summarized in table 1. The biopsy specimens obtained from 11 of the smokers and two of the nonsmokers were not good enough to allow determination of the activator activity. One of the blood samples obtained for determination of the fibrinolytic activity after the venous occlusion was lost by accident. No significant difference was found between the groups when either the fibrinolytic activator activity in superficial hand veins or fibrinolytic activity after venous occlusion of the forearms was measured.

Effect of Abstention from Smoking on Fibrinolytic Activity Following Venous Occlusion and on Fibrinolytic Activator Activity in Superficial Hand Veins

The results after one week's abstention are given in table 2. One blood sample obtained for determination of fibrinolytic activity after venous occlusion was lost by accident. The comparison of the fibrinolytic activity following venous occlusion is therefore based on 18 individuals. The preparation of six biopsy specimens proved unsuccessful. The comparison of the fibrinolytic activator activity in superficial hand veins is therefore based on 13 individuals. The fibrinolytic activity following venous occlusion and the fibrinolytic activator activity of the superficial veins tended to be lower but the difference was not significant.

At check-examination three participants were found to have a carbon monoxide hemoglobin above 1% and were therefore excluded from the comparison after eight to nine weeks' abstention. Preparation of six of the biopsy specimens from those who had refrained from smoking and nine of the re-examined controls

Table 2
Effect of Smoking Cessation over Eight to Nine Weeks on the Fibrinolytic Activity*

<table>
<thead>
<tr>
<th></th>
<th>After VO†</th>
<th>In SV†</th>
</tr>
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<tbody>
<tr>
<td>I. Initial value</td>
<td>179 ± 29</td>
<td>6.3 ± 0.2</td>
</tr>
<tr>
<td>II. After 1 week’s smoking cessation</td>
<td>153 ± 24</td>
<td>5.5 ± 0.4</td>
</tr>
<tr>
<td>III. After 8–9 weeks’ smoking cessation</td>
<td>189 ± 24</td>
<td>6.2 ± 0.5</td>
</tr>
<tr>
<td>P I – II</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>P I – III</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>P II – III</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Values are means ± standard errors.
†Fibrinolytic activity after venous occlusion (VO) (lysed area in mm²).
‡Fibrinolytic activity in superficial veins (SV) (arbitrary units).
NS = not significant.
proved unsuccessful. Among the resulting groups compared, fibrinolytic activity measured after venous occlusion or in biopsy specimens did not differ significantly from the initial recordings in either the control group or the smokers.

When comparing fibrinolytic activity after one week's smoking cessation and after 8-9 weeks' smoking cessation in the randomly selected subsample of 19 individuals, the fibrinolytic activity tended to be higher both after venous occlusion and in the biopsy specimens (table 2). Out of these 19 individuals one was excluded from the follow-up because of a COHb value of more than 1%. The comparison of the fibrinolytic activity following venous occlusion is therefore based on 18 individuals. Six biopsy specimens had proved unsuccessful at the follow-up after one week's abstention from tobacco and the comparison of activator activity in superficial veins is therefore based on 13 individuals. No significant differences were found when comparing initial values in those 19 individuals with the whole group of abstainers.

Effect of Smoking Six Cigarettes on the Fibrinolytic Activity after Venous Occlusion and on the Fibrinolytic Activator Activity of Superficial Veins

The results are given in table 3. The fibrinolytic activator activity of superficial veins increased significantly. The fibrinolytic activity after venous occlusion tended to increase but not significantly. The fibrinolytic activity measured as euglobulin clot lysis time increased significantly. Other variables assessed to estimate the immediate effect of smoking, i.e., FDP, platelet count, platelet adhesiveness, APTT, AHF, and fibrinogen in the smokers did not change after smoking.

Discussion

Physical exertion raises the fibrinolytic activity in the blood, as does injection of vasoactive drugs such as adrenalin, nicotine acid, and vaso-pressin. But injection of such substances has not been found to have any effect on the activator activity in the superficial veins. The effect of smoking on the vascular tree is reflected in an increase in the pulse rate, in the blood pressure, and in the fibrinolytic activity of the blood.

No difference in either fibrinolytic activity after venous occlusion of the forearms or activator activity in superficial veins was found between these randomly selected male heavy smokers and nonsmokers of uniform age. The earlier findings of a lower fibrinolytic activity in smokers as compared to nonsmokers may be explained by differences in the experimental conditions and examination methods used. The fibrinolytic activity in the blood as well as the fibrinolytic activator activity in the vessel walls tended to fall on abstention from smoking, but no significant differences were recorded.

The concentration of COHb increased after consumption of six cigarettes from, on an average, 1.9 to 3.5%. Astrup and Kjeldsen elucidated the effect of carbon monoxide on the vessel endothelium in animal experiments. Using scanning electron microscopy they found an increase in carbon monoxide concentration to be accompanied by a subendothelial edema which, according to Astrup, probably is due to an increased vascular permeability. The increased fibrinolytic activator activity of the vessel wall after six cigarettes might be explained on this basis.

Smoking appeared to have no effect on platelet adhesiveness or on the concentration of coagulation factors, i.e., it was not possible to confirm the increased coagulation tendency or platelet adhesiveness reported by Engelberg and Levine. The discrepancy between the results may, however, be explained by differences in the experimental conditions and examination methods used.

References

8. Isackson SO: Venous occlusion plethysmography in 55-year-old

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Table 3

Effect of Smoking on Fibrinolytic Activity*

<table>
<thead>
<tr>
<th></th>
<th>After VO†</th>
<th>In SV‡</th>
<th>Euglobulin clot lysis time (min)</th>
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<tbody>
<tr>
<td></td>
<td>N = 19</td>
<td>N = 19</td>
<td>N = 19§</td>
</tr>
<tr>
<td>Initial value</td>
<td>253 ± 29</td>
<td>5.3 ± 0.3</td>
<td>332 ± 19</td>
</tr>
<tr>
<td>After six cigarettes</td>
<td>288 ± 24</td>
<td>6.3 ± 0.2</td>
<td>260 ± 12</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Values given are means ± standard errors.
†Fibrinolytic activity after venous occlusion (VO) (lysed area in mm²).
‡Fibrinolytic activity in superficial veins (SV) (arbitrary units).
§Missing data in one subject.
NS = not significant.
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22. Janzon L: The acute effect of smoking on calf blood flow. A plethysmographic study in heavy smokers. VASA 1974
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