Cigarette Smoking and Hypertension
Factors Independently Associated with Blood Hyperviscosity and Arterial Rigidity

Jaime Levenson, Alain C. Simon, François A. Cambien, and Christine Beretti

The effects of cigarette smoking and hypertension on hemorheological variables (blood viscosity over a wide range of shear rates, plasma viscosity, microhematocrit, and plasma protein concentration) and on arterial stiffness (pulse wave velocity) were investigated in 33 normotensive men and 81 mild to moderately hypertensive men. Of these, 22 normotensive and 24 hypertensive subjects were cigarette smokers. Cigarette smoking and hypertension were independently associated with higher blood viscosity at all studied shear rates (from 0.2 to 241 sec⁻¹) as well as with higher plasma viscosity, hematocrit, and pulse wave velocity. At constant hematocrit levels, hypertension remained associated with a higher blood viscosity, while the association with cigarette smoking disappeared. Normotensive smokers had the same increase in blood and plasma viscosity and pulse wave velocity as hypertensive nonsmokers. No interactive effects of hypertension or cigarette smoking on blood or arterial variables were observed, suggesting that the effect of these two factors on blood and vascular rheology are cumulative. Smoking and hypertension may change the flow properties of the blood and the behavior of the arterial wall and this may explain the arterial damage observed in cigarette smokers and hypertensive patients. (Arteriolecreals 7:572–577, November/December 1987)

Although the association of smoking and hypertension with increased cardiovascular morbidity and mortality is a generally accepted fact,¹ the mechanisms by which these factors are linked to cardiovascular damage are not yet clarified. Changes in shear force imposed on the arterial wall and its endothelial lining by the neological disturbances of blood flow caused by smoking and hypertension could play an important role in the pathogenesis of arterial disease. Several hemorheological abnormalities have been reported in hypertensive patients who may have raised hematocrit⁶,⁷ and fibrinogen⁴,⁵ as well as increased plasma and blood viscosity.⁴,⁶,⁷,⁸ Similar abnormalities have been observed in cigarette smokers.⁹,¹⁰,¹¹ On the other hand, increased intraluminal pressure caused by changes in the physical properties of the arterial wall may contribute to the degenerative process of the arteries. Decreased arterial compliance¹² and increased pulse wave velocity¹³,¹⁴ taken as a simple index of arterial stiffness are associated with hypertension in men, but no study has analyzed the arterial consequences of cigarette smoking using these parameters. Furthermore, the independent and cumulative effects of hypertension and cigarette smoking on blood and arterial rheological properties have not been properly investigated. Thus, the present study was undertaken to determine whether cigarette smoking could induce blood hyperviscosity and arterial rigidity in normotensive and in mild to moderately hypertensive men.

Methods

A cross-sectional study was carried out on 114 male subjects; 81 men had mild to moderate hypertension (I and V Korotkoff sounds above 140/90 mm Hg), and the 33 others were healthy volunteers. All the subjects were untreated or had been withdrawn from treatment at least 4 weeks before the study. None had cardiac, neurological, or renal complications or peripheral vascular disease; the essential hypertension was documented by standard laboratory tests and timed intravenous pyelography. The clinical and biological tests in the controls (serum and urinary electrolytes, serum creatinine, electrocardiogram and chest x-ray) were normal. Control subjects received no medication. The protocol was approved by INSERM (Institut National de la Santé et de la Recherche Médicale). Informed consent for the investigation was obtained from each subject.

Normotensive and hypertensive subjects were classified as smokers or nonsmokers according to their cigarette smoking habits. For the purpose of this study, a cigarette smoker was defined as someone who had regularly smoked at least five cigarettes per day for the previous 3 months. Subjects who smoked less than this or who smoked cigars or a pipe were excluded from the statistical analysis. Among the 33 healthy controls, 11 were nonsmokers and 22 were smokers, while among the 81 hypertensive patients, 57 were nonsmokers and 24 were smokers. Systemic blood pressure was measured with a sphygmomanometer three times in reclining subjects.

Blood samples were obtained from the antecubital vein.
Table 1. Clinical Characteristics of Normotensive and Hypertensive Subjects According to Cigarette Smoking

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Healthy controls</th>
<th>Hypertensive patients</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonsmokers n = 11</td>
<td>Smokers n = 22</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>42 ± 4</td>
<td>44 ± 2</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78 ± 3</td>
<td>76 ± 2</td>
<td></td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>119 ± 3</td>
<td>159 ± 2</td>
<td>0.05 NS</td>
</tr>
<tr>
<td>Diastolic</td>
<td>73 ± 2</td>
<td>101 ± 1</td>
<td>0.05 NS</td>
</tr>
<tr>
<td>Pulse rate (beats/min)</td>
<td>63 ± 3</td>
<td>72 ± 2</td>
<td>0.001 NS</td>
</tr>
</tbody>
</table>

|                     | Nonsmokers n = 57      | Smokers n = 24        |                 |
| Age (yrs)           | 43 ± 1                 | 42 ± 2                |                 |
| Weight (kg)         | 78 ± 2                 | 78 ± 2                |                 |
| Blood pressure (mm Hg) |                       |                       |                 |
| Systolic            | 126 ± 2                | 161 ± 3               | 0.05 NS         |
| Diastolic           | 80 ± 2                 | 101 ± 1               | 0.05 NS         |
| Pulse rate (beats/min) | 66 ± 2                | 76 ± 2                | 0.01 NS         |

Values are means ± SEM. NS = not significant.

by clean venepuncture with disposable needles and plastic syringes between 8 A.M. and 10 A.M. after an overnight fast. Blood was treated with dry potassium EDTA anticoagulant and was used for the determination of blood viscosity, plasma viscosity, microhematocrit, and plasma protein concentration. Plasma was obtained by centrifugation at 3000 g for 15 minutes. Blood viscosity refers here to an "apparent viscosity" since blood as a non-Newtonian fluid does not possess a constant viscosity at all shear rates. Blood viscosity was determined in all subjects with a couette viscometer with coaxial cylinders (Low Shear 30, Contraves AG, Zurich) which allowed measurement by 30 discrete values over a wide range of shear rates varying from 0.033 sec⁻¹ to 241 sec⁻¹. The measurements were taken at shear rates of 241, 52, 11, 2.4, 0.52, and 0.2 inverse seconds (sec⁻¹) and were expressed as milliPascal per second (mPa/sec). Plasma viscosity was determined as the average of three measured shear rates (52, 2.4, and 0.2 sec⁻¹) because of its shear rate-independent characteristics. All measurements were performed at 37°C by branching the viscosimeter cylinder containing the blood sample to a circulating bath thermostat. Plasma protein concentrations were determined with a refractometer. Microhematocrit was determined in duplicate by use of a Hawksley centrifuge (12,000 g for 3 minutes).

Pulse wave velocity along the brachial and radial arteries was measured with two transcustaneous strain gauge transducers (VR12 Simultrace Recorder, Electronics for Medicine, Pleasantville, New York) fixed to the skin over the most prominent part of the brachial and radial arteries. The foot-to-foot arterial wave velocity was calculated as the ratio between the distance separating the two transducers and the time interval separating the feet of the brachial and radial waves. The brachial and radial pulses were recorded simultaneously at a paper speed of 150 mm/sec, and the foot of the wave was defined as the point of intersection of the line extrapolating the last part of diastole of the preceding curve and the line extrapolating the early part of systole. This time interval was measured in at least 10 pairs of pulses, and the mean value was used to

Figure 1. Plasma viscosity, plasma protein concentrations, and hematocrit in normotensive and hypertensive nonsmokers and smokers. Values are mean ± SEM. NS = not significant.
Figure 2. Determination of blood viscosity over a wide range of shear rates in normotensive and hypertensive nonsmokers and smokers. Values are mean ± SEM. NS = not significant.
calculate pulse wave velocity in meters per second; the reproducibility of the method was 8% ± 5%.18

Statistical Analysis

Group data were expressed as means ± SEM. Differences between groups for blood and arterial variables were assessed by Student's t tests and by a two-way analysis of variance. In the latter case, hypertension and cigarette smoking were used as grouping factors, and a simultaneous adjustment on covariates was performed. The interaction between hypertension and cigarette smoking was also tested in the analysis of variance. The statistical package BMPD 2V19 was used to perform this analysis. A p value less than 0.05 was considered significant.

Results

Clinical Characteristics of the Population

As shown in Table 1, normotensive and hypertensive subjects (smokers and nonsmokers) had similar ages and weights. Systolic and diastolic blood pressures were by definition greater in the hypertensive group (smokers and nonsmokers) than in the control group. Heart rate was also faster in hypertensive patients (smokers and nonsmokers). Normotensive smokers had slightly higher systolic and diastolic blood pressures (p < 0.05) than the normotensive nonsmokers.

Cigarette Smoking in Normotensive Subjects

Plasma viscosity was slightly higher in smokers than in nonsmokers (p < 0.05). Total plasma protein concentrations were elevated in smokers (p < 0.01) (Figure 1). Blood viscosity was higher in smokers than in nonsmokers, and the extent of this increase was inversely related to shear rate. At high shear rates (52 to 241 sec⁻¹), blood viscosity was approximately 10% to 12% higher in smokers than in nonsmokers, while at lower shear rates (0.2 to 11 sec⁻¹) the difference was between 15% and 20% (Figure 2). The hematocrit values were higher (p < 0.001) in smokers than in nonsmokers (Figure 1). Pulse wave velocity values demonstrated slightly more arterial rigidity in smokers than in nonsmokers (p < 0.05) (Figure 3).

Cigarette Smoking in Hypertensive Patients

Plasma viscosity and total plasma protein concentration were similar in smoking and nonsmoking hypertensive subjects (Figure 1). In contrast, a 4% elevation in blood viscosity at higher shear rates (52 to 241 sec⁻¹) and a 10% elevation at lower shear rates (0.2 to 11.2 sec⁻¹) was observed in hypertensive smokers (Figure 2). Hematocrit was also significantly higher (p < 0.05) in hypertensive smokers than in the hypertensive nonsmokers (Figure 1). A similar significant increase (p < 0.05) was observed for the pulse wave velocity in hypertensive smokers (Figure 3).

Comparison between Normotensive and Hypertensive Subjects

In nonsmokers, hypertension was associated with higher plasma viscosity (p < 0.01) and higher total protein concentrations (p < 0.05, Figure 1) and with increased blood viscosity (from approximately 11% to 13% at higher shear rates to 17% to 23% at lower shear rates) (Figure 2). Furthermore, hypertensive nonsmokers had slightly higher hematocrit values than normotensive nonsmokers (p < 0.05, Figure 1). Pulse wave velocity was much higher (36%) in hypertensive nonsmokers than in normotensive nonsmokers (p < 0.001, Figure 3).

Among smokers, hypertensive subjects had a slightly higher blood viscosity at all shear rates measured (4% to 11%, p < 0.05) than normotensive subjects, but hematocrit plasma viscosity and total plasma protein concentrations were not different (Figures 1 and 2). Arterial rigidity was 16% higher in hypertensive smokers than in normotensive smokers (p < 0.05).

The comparison of normotensive smokers with hypertensive nonsmokers showed that there were no significant differences in any rheological parameter or in pulse wave velocity. In contrast, significant differences were obtained when normotensive nonsmokers were compared with hypertensive smokers (Figures 1, 2, and 3).

Analysis of Simultaneous Effects of Smoking and Hypertension

Our analysis of variance of blood variables with simultaneous adjustment for age and weight using hypertension and cigarette smoking as grouping factors showed that these two factors were independently associated with higher blood viscosity, hematocrit, and plasma viscosity.
viscosity observed in hypertensive and normotensive smokers is an original finding; indeed, the fact that healthy inverse shear rate-related increase in blood viscosity in male smokers have increased levels of blood viscosity was less than those at lower shear rates. This reported by

Because blood viscosity is a function of hematocrit and plasma viscosity (which itself is related to proteins), an analysis of these parameters in which blood viscosity was adjusted to constant values of hematocrit, proteins, and plasma viscosity were also performed. When hematocrit remained constant, hypertension continued to be associated with a higher blood viscosity; this association disappeared with cigarette smoking (Table 2). Hypertension and cigarette smoking were also independently associated with a higher pulse wave velocity (Table 2). There was no interactive effect on blood and arterial variables between hypertension and cigarette smoking, suggesting a cumulative effect of these two factors on blood and on vascular rheology.

### Discussion

There is growing interest in the part played by altered blood viscosity and large artery walls in vascular degenerative damage. The present study was designed to evaluate the relative effects of high blood pressure and cigarette smoking on blood and vascular rheology. Since blood viscosity varies according to the size of the vessel and the rate of blood flow, we measured this parameter at different gradient velocities of blood (shear rates). At a low shear rate, which can be assumed to correspond schematically to low flow conditions, the red cells aggregate to form rouleaux, and therefore this measurement yields an index of the degree of red cell aggregation. At the lower shear rates (Figure 2), blood viscosity was significantly higher in both normotensive and hypertensive smokers than in nonsmokers. At the higher shear rates provided by our device (which approximate those found in the precapillary vessels of normal subjects) the increase in blood viscosity observed in hypertensive and normotensive smokers was less than those at lower shear rates. This inverse shear rate-related increase in blood viscosity in smokers is an original finding; indeed, the fact that healthy male smokers have increased levels of blood viscosity was reported by Dintenfass and Lowe et al. who determined blood viscosity at a unique shear rate. Elevated blood viscosity was also found in the hypertensive patients of our study (both smokers and nonsmokers) and this elevation was inversely related to shear rate as previously reported by Letcher et al. Although our study confirms the well known increase of hematocrit associated with hypertension and cigarette smoking, the role of high hematocrit as a factor inducing raised blood viscosity was not the same in hypertensive patients as in cigarette smokers. The analysis of the simultaneous effects of smoking and hypertension on blood viscosity and hematocrit showed that when these variables were adjusted to one other, only hypertension remained associated with a higher blood viscosity at a constant hematocrit. This result may indicate that blood hyperviscosity in hypertensive patients is related to factors other than increased hematocrit; in cigarette-smoking patients, the higher hematocrit might explain the elevated blood viscosity.

Another goal of our study was to assess the influence of plasma proteins on the increased viscosity associated with hypertension and cigarette smoking. The mean values of plasma viscosity and total plasma protein concentration were increased in both normotensive smokers and hypertensive nonsmokers, but there was no independent association of hypertension and cigarette smoking with higher protein concentration at constant ages and weights. This result is consistent with the results of Letcher et al. who found that total protein concentration, as well as plasma viscosity, were higher in hypertensive patients; however, these researchers did not adjust these variables to constant age and weight. This group also demonstrated the effect of increased fibrinogen concentration on blood viscosity; patients' blood viscosity was similar to that of normal subjects only when their blood was defibrinated. Fibrinogen elevation is not restricted to hypertension, but also occurs in smokers as shown in several studies, so that further study of fibrinogen plasma levels will be needed to clarify the data in the present study. In fact, a major purpose of our study was to investigate the mecha-

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<td>0.001</td>
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<td>52 sec⁻¹</td>
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<tr>
<td>2.4 sec⁻¹</td>
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<td>0.01</td>
<td>0.0005</td>
<td>0.05</td>
</tr>
<tr>
<td>0.52 sec⁻¹</td>
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<td>0.02</td>
<td>0.001</td>
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<tr>
<td>0.2 sec⁻¹</td>
<td>0.02</td>
<td>0.18</td>
<td>0.01</td>
<td>0.02</td>
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Values are p values. Variables were adjusted to constant values of age (A), weight (W), hematocrit (Ht), proteins (P), and plasma viscosity (PV).
nisms of the association between cigarette smoking and hypertension on blood rheological abnormalities. Our finding that normotensive smokers had the same increase in blood and plasma viscosity as hypertensive nonsmokers is an original finding and indicates that these factors can independently modify the blood flow properties of the vessels. The interactive effect of hypertension and cigarette smoking on increased blood viscosity at all shear rates and on increased hematocrit and plasma viscosity was not statistically significant, suggesting a cumulative effect of these rheological variables. The impairment of the flow properties of blood might be a mechanism for arterial damage. If so, this agrees with the epidemiological evidence that hypertension and cigarette smoking are cumulative risk factors for atherosclerotic disease.

Another original finding of the present study is the increased pulse wave velocity (i.e., arterial rigidity) observed in normotensive healthy smokers in comparison with normotensive nonsmokers. Among the mechanisms that may contribute to increased arterial rigidity of the large arteries are arterial pressure level and age because these two variables can change the properties of the large arteries. The slightly higher blood pressure (5%) observed in normotensive smokers does not by itself explain the 21% increase in pulse wave velocity when compared to normotensive nonsmokers. Moreover, pulse wave velocity was 7% higher in hypertensive smokers when compared to hypertensive nonsmokers despite similar blood pressure levels in the two hypertensive subgroups. Arterial aging might also contribute to the increased arterial stiffness in hypertension. We have recently reported evidence of early degenerative changes in large arteries in human hypertension using pulse wave velocity analysis; this suggests that other degenerative factors associated with the natural aging process might help to alter the arterial function. Even though in the present study the subjects were about the same age, hypertension and cigarette smoking were adjusted on age by introducing this covariate in the analysis of variance to avoid any possible age-induced arterial rigidity. By controlling age and weight, we observed that hypertension and cigarette smoking were independently associated with higher pulse wave velocity, but that the effect was cumulative for increased arterial stiffness.

In conclusion, the main finding of this study is that hypertension and smoking affect the flow properties of blood and arterial wall behavior. This is characterized by several hemorheological abnormalities (increased blood and plasma viscosity, hematocrit, and proteins) and arterial stiffness (increased pulse wave velocity). Mass screening in prospective epidemiological studies can use newly available techniques to detect these abnormalities before vascular degenerative damage can occur.

Acknowledgment

The skilled secretarial assistance of Christine Beuzet is gratefully acknowledged.

Index Terms: cigarette smoking · arterial hypertension · blood and plasma viscosity · arterial stiffness · cardiovascular risk factors

References

Cigarette smoking and hypertension. Factors independently associated with blood hyperviscosity and arterial rigidity.
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Arterioscler Thromb Vasc Biol. 1987;7:572-577
doi: 10.1161/01.ATV.7.6.572
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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