Elevated Blood Viscosity in Patients with Borderline Essential Hypertension

ROBERT L. LETCHER, M.D., SHU CHIEN, M.D., PH.D., THOMAS G. PICKERING, M.D., D.PHIL., AND JOHN H. LARAGH, M.D.

SUMMARY In patients with borderline hypertension, total peripheral resistance (TPR) is either elevated or abnormally related to cardiac output. Since blood viscosity is one determinant of TPR, we compared various components of blood viscosity in 25 patients with borderline hypertension and 25 normal subjects. Under all experimental blood flow conditions examined, blood viscosity directly correlated with systolic and diastolic blood pressure ($p < 0.05$ or better) and was greater in the hypertensive than in normal subjects. Venous hematocrit and plasma viscosity were higher in the hypertensive patients. These latter rheologic abnormalities accounted for the increased blood viscosity at higher shear rates. At lower shear rates, increased red cell aggregation, primarily mediated by elevated fibrinogen concentration, accounted for the higher blood viscosity in the hypertensive subjects. We conclude that even relatively small elevations in arterial pressure are associated with increased viscous resistance of blood to flow, and that the increased blood viscosity is a consequence of increased hematocrit, plasma viscosity, and red cell aggregation. (Hypertension 5: 757-762, 1983)

KEY WORDS • fibrinogen • hyperviscosity • shear rate • hematocrit

MILD or borderline hypertension is a disorder in which blood pressure is above the normal range, but the levels may not be sufficiently high to warrant pharmacologic treatment. This type of hypertension has attracted investigative interest not only because of its clinical value as the most reliable predictor of future established hypertension, but also because the early biochemical and hemodynamic alterations observed may be causally related to initiation of the blood pressure elevation. These alterations are not simply a reflection of secondary, pressure-related changes that occur as a consequence of established hypertension.

A number of abnormalities have been reported in patients with borderline hypertension. Cardiac output is elevated in about one-third, and most evidence indicates that this increase is mediated via the sympathetic nervous system. Plasma volume may be normal or decreased. Plasma renin activity (PRA) and 24-hour urinary sodium excretion are related in a manner similar to that found in patients with established hypertension. By mechanisms that remain incompletely understood, total peripheral resistance is abnormally elevated in relation to systemic blood flow.

Since blood viscosity is one factor that determines vascular resistance and blood flow, we examined the components of blood viscosity in a group of 25 patients with untreated borderline essential hypertension and compared these to similar measurements obtained in 25 normal subjects. The results show that borderline hypertension is associated with elevated blood viscosity and, at the blood flow conditions prevailing in the circulatory system, blood viscosity is directly correlated with the systolic and diastolic blood pressures. These findings indicate that rheological changes accompany even marginal elevations in blood pressure, and are therefore consistent with the viewpoint that complex physiologic aberrations are already operative during the development of borderline hypertension.
Methods

Patients

Twenty-five adults whose diastolic blood pressure was less than 90 mm Hg at the time of examination constitute the control group. None of these subjects gave a history of cardiovascular, renal, hepatic, endocrine, or hematological disorders. Laboratory tests confirmed that hemoglobin, hematocrit, plasma electrolytes, and creatinine concentrations as well as the red cell indices and urinalysis were normal in all cases. Liver function tests (including serum glutamic oxaloacetic transaminase (SGOT), gamma glutamyl transpeptidase (GGTP), alkaline phosphatase, and bilirubin concentrations), fasting blood glucose and lipid levels were likewise within the normal range. None was receiving any medications (including oral contraceptives) at the time of the study.

Twenty-five adults who were undergoing evaluation in the outpatient facilities of the Hypertension Center at The New York Hospital were age- and sex-matched with this normal population. These patients gave a history of elevated arterial blood pressure and were found to have at least one of three office diastolic blood pressure measurements below 90 mm Hg, and one or more between 90 and 105 mm Hg on three different examinations. None of these patients had received any antihypertensive medications or other drugs for at least 2 weeks preceding the pressure readings and viscosity studies. Appropriate laboratory investigations were performed to exclude patients with coexistent cardiac, hepatic, renal, endocrine, or hematological disorders. A thorough physical examination failed to reveal signs of hypertensive target organ disease, and all had normal ophthalmoscopic examinations of the retinal vasculature. This group of patients was considered to have borderline hypertension.

Analytical Methods

Hemodynamic Variables

Arterial blood pressure and heart rate were measured in the seated position. Disappearance of Korotkoff phase 1 and 5 sounds was taken as indicating the disappearance of blood pressure. Twenty-five subjects with systolic and diastolic blood pressures, respectively.

After the hemodynamic measurements, blood was obtained without stasis through an indwelling venous catheter. Heparinized blood was used for the rheological analyses (described below), all of which were completed within 4 hours of sampling. Blood for determination of plasma renin activity was collected into tubes containing potassium EDTA; each specimen was kept at 30°C until assayed. During collection of a complete 24-hour urine, the urine was stored at -4°C for measurement of urinary aldosterone. Twenty-five adults undergoing evaluation at The New York Hospital were age- and sex-matched with this normal population.

Hematological Analyses

The microhematocrit was determined in duplicate by centrifuging at 15,000 g for 5 minutes, and was corrected for plasma trapping. Plasma renin activity (PRA) was quantitated by radioimmunoassay of the angiotensin I formed after a 3-hour incubation of EDTA plasma at pH 5.7. An 18-hour incubation was performed when the renin activity was less than 1.0 ng/ml/hr. Daily urinary aldosterone excretion was determined by radioimmunoassay of a 24-hour urine collection.

Plasma Protein Analyses

Total plasma protein concentrations were determined at 37°C using a Bausch and Lomb refractometer. Plasma fibrinogen concentration was estimated in aliquotes of heparinized plasma using the method of Ratnoff and Menzie. Plasma protein fractions were determined by microzone electrophoresis on cellulose acetate strips.

Viscosity Measurements

A couette viscometer was used, which had the sensitivity and precision necessary for measurement of blood viscosity over a wide range of shear rates. Blood viscosity (ηB) was determined at shear rates of 208, 104, 52, 5.2, 0.5, and 0.1 sec-1. Plasma viscosity was measured at 52 and 0.5 sec-1 and, since this rheological variable is shear rate independent, the results obtained were averaged. All viscosity measurements were performed at 37°C.

Renin and Aldosterone Measurements

Plasma renin activity (PRA) was quantitated by radioimmunoassay of the angiotensin I formed after a 3-hour incubation of EDTA plasma at pH 5.7. An 18-hour incubation was performed when the renin activity was less than 1.0 ng/ml/hr. Daily urinary aldosterone excretion was determined by radioimmunoassay of a 24-hour urine collection.

Other Biochemical Analyses

Daily electrolyte intake was estimated through measurement of 24-hour urine sodium and potassium. Plasma osmality was measured on an automatic osmometer (Advanced Instruments, Waltham, Massachusetts). Plasma and 24-hour urine creatinine concentrations were also determined.

| TABLE 1. Comparison of Age, Hemodynamic and Biochemical Variables in Normal Subjects and Patients with Borderline Hypertension |
|-----------------|------------------|---------------|-----------|
| Variable        | Normal subjects  | Borderline hypertension |
| Age (yrs)       | 40 ± 10          | 41 ± 12       | NS        |
| SBP (mm Hg)     | 115 ± 10         | 145 ± 9       | <0.01     |
| DBP (mm Hg)     | 78 ± 8           | 94 ± 5        | <0.01     |
| Heart rate (min-1) | 70 ± 13        | 79 ± 14       | <0.05     |
| UNa⁺V (mEq/day) | 155 ± 77         | 145 ± 66      | NS        |
| UK⁺V (mEq/day)  | 72 ± 20          | 78 ± 26       | NS        |
| U Aldo (µg/day) | 8.2 ± 5.1        | 11.6 ± 6.2    | NS        |
| PRA (ng/ml/hr)  | 2.0 ± 1.2        | 2.0 ± 1.4     | NS        |

All values expressed as means ± so. SBP = systolic blood pressure; DBP = diastolic blood pressure; UNa⁺V = daily urinary sodium excretion; UK⁺V = daily urinary potassium excretion; PRA = plasma renin activity.
Results

There were 18 men and seven women in both the normal and hypertensive groups. The 25 control subjects had a mean age of 40 ± 10 years (± SD) (range = 26–64 years), which was similar to that of the hypertensive patients (mean = 41 ± 12 years; range = 23–68) (table 1). The groups were also similar with respect to plasma renin activity (PRA) and daily urinary electrolyte composition. The slightly higher 24-hour urinary aldosterone excretion level in the borderline hypertensive group did not reach statistical significance. Systolic and diastolic blood pressures were, by definition, greater (p < 0.01) in the patients with borderline hypertension than in the control subjects; heart rate was also greater in these patients.

Plasma viscosity (ηp) was slightly higher in the hypertensive than in the normal subjects (table 2), and there were positive correlations between plasma viscosity and total plasma protein (r = 0.688, p < 0.001), total plasma globulin (r = 0.751, p < 0.001), and fibrinogen (r = 0.345, p < 0.05) concentrations. Plasma viscosity did not correlate with plasma albumin concentration (p > 0.1). Among all 50 subjects, multiple linear regression analysis was used to determine which of the plasma protein fractions made the greatest contribution to plasma viscosity. Fibrinogen (φ) and beta-2 (β2) globulin concentrations were identified as having the greatest regression coefficients: r| p = 0.14a, + 0.14a 2 + 0.13β, + 0.22β 2 + 0.07γ + 0.18φ + 0.88. When the five globulin fractions were considered separately, multiple regression analysis further demonstrated that the beta-1 (β1) and beta-2 (β2) protein fractions contributed relatively more to the globulin influence on plasma viscosity than did the alpha-1 (α1), alpha-2 (α2), or gamma (γ) globulin fractions: ηp = -0.14α1 + 0.17α2 + 0.21β1 + 0.07γ + 0.9. When all globulin fractions are considered together (total globulins), the influence of a unit change in total globulin concentration on plasma viscosity is slightly less than a unit change in fibrinogen concentration: ηp = 0.15φ + 0.13 [total globulin] + 0.86.

Blood viscosity was elevated in patients with borderline hypertension as compared to control subjects (table 3), and the extent of this increase was inversely related to shear rate. At high shear rates (208–52 sec⁻¹), blood viscosity was approximately 6% to 8% higher in hypertensive subjects, while at lower shear rates (5.2 – 0.1 sec⁻¹), the difference was between 14% and 22%. The differences in blood viscosity may be attributed to both increased hematocrit (43.4% ± 2.0% vs 41.0% ± 2.5%, p < 0.02) and plasma viscosity (1.27 ± 0.06 cPvs 1.23 ± 0.04 cPs, p < 0.01) in the hypertensive group. The relative blood viscosity (ηp/ηp), which expresses the contribution of the red cells to blood viscosity independently of the direct rheologic effect of plasma viscosity, was slightly higher (p < 0.05) in the hypertensive patients at high shear rates of 52 and 104 sec⁻¹. At lower shear rates (≤ 5.2 sec⁻¹), the elevation in relative blood viscosity in hypertensive patients was of greater statistical significance (p < 0.01) (table 4).

<table>
<thead>
<tr>
<th>Table 2. Determinants of Plasma Viscosity in Normal Subjects and in Patients with Borderline Hypertension</th>
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</thead>
<tbody>
<tr>
<td>Subjects</td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>Normal (n = 25)</td>
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<tr>
<td>Borderline hypertensive (n = 25)</td>
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</table>

All values expressed as means ± sd.

<table>
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<tr>
<th>Table 3. Comparison of Hematocrit and Blood Viscosity in Normal Subjects and in Patients with Borderline Hypertension</th>
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<tbody>
<tr>
<td>Subjects</td>
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<tr>
<td></td>
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<td>Borderline hypertensive (n = 25)</td>
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</tbody>
</table>

All values are expressed as means ± sd.
In normal and hypertensive subjects, systolic and diastolic blood pressures were directly correlated with blood viscosity at each shear rate tested (table 5). As shown in table 6, relative blood viscosity and systolic and diastolic blood pressures correlated only at lower shear rates, when the direct rheologic effects of plasma viscosity ($\eta_p$) are factored out of whole blood viscosity ($\eta_b$) by computing relative blood viscosity ($\eta_{rb}$).

### Discussion

Certain biochemical and hemodynamic abnormalities have been described in patients with borderline hypertension\(^1\:\: 2\:\: 3\:\: 9\) The fundamental hemodynamic abnormality seems to be an elevated total peripheral resistance at a given cardiac output.\(^6\:\: 10\:\: 11\) The mechanism of this elevation has not yet been fully elucidated. Since the viscous resistance of the blood to flow and the degree of arteriolar vasoconstriction determine total peripheral resistance,\(^11\) this study was undertaken to establish whether the flow properties of blood contributed to the elevation in blood pressure.

Blood viscosity was increased in patients with borderline hypertension under all flow conditions examined (table 3). The extent to which blood viscosity was elevated, and the rheologic abnormalities that accounted for the elevation, were dependent upon these conditions. At high shear rates ($\geq 52$ sec$^{-1}$), blood viscosity is largely determined by hematocrit and plasma viscosity.\(^11\:\: 14\:\: 18\) Compared to normotensive subjects, patients with borderline hypertension had elevated hematocrit levels ($p < 0.02$) and increased plasma viscosity ($p < 0.01$) (tables 2 and 3). Thus, the increased viscous flow resistance at high shear rates in patients with borderline hypertension was primarily a consequence of increased hematocrit and plasma viscosity.

Relative blood viscosity ($\eta_{rb}$) is the ratio of the viscosity of blood ($\eta_b$) to plasma viscosity ($\eta_p$), and it reflects primarily the rheologic behavior of the cells. Shear rate is directly proportional to the ratio of blood flow velocity to blood vessel diameter,\(^18\:\: 23\:\: 25\) and the

### Table 4. Comparison of Hematocrit and Relative Blood Viscosity in Normal Subjects and in Patients with Borderline Hypertension

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Hct (%)</th>
<th>208</th>
<th>104</th>
<th>Shear rate (sec$^{-1}$)</th>
<th>52</th>
<th>5.2</th>
<th>0.5</th>
<th>0.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (n = 25)</td>
<td>41.0 ± 2.5</td>
<td>3.27 ± 0.25</td>
<td>3.42 ± 0.26</td>
<td>3.74 ± 0.30</td>
<td>6.44 ± 0.94</td>
<td>19.7 ± 4.2</td>
<td>43.9 ± 8.5</td>
<td></td>
</tr>
<tr>
<td>Borderline hypertensive (n = 25)</td>
<td>43.4 ± 2.0</td>
<td>3.38 ± 0.23</td>
<td>3.66 ± 0.26</td>
<td>3.92 ± 0.29</td>
<td>7.13 ± 0.72</td>
<td>23.3 ± 3.8</td>
<td>51.0 ± 8.6</td>
<td></td>
</tr>
<tr>
<td>Difference (%)</td>
<td>3.2</td>
<td>7.0</td>
<td>4.8</td>
<td>10.7</td>
<td>18.3</td>
<td>16.2</td>
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</table>

All values are expressed as means ± SD.

### Table 5. Computed Correlation Coefficients Relating Blood Viscosity to Systolic and Diastolic Blood Pressures in Normal Subjects and in Patients with Borderline Essential Hypertension (n = 50)

<table>
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<tr>
<th>Blood pressure</th>
<th>SBP</th>
<th>DBP</th>
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<tr>
<td>SBP</td>
<td></td>
<td></td>
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<td>DBP</td>
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### Table 6. Computed Correlation Coefficients Relating Relative Blood Viscosity to Systolic and Diastolic Blood Pressures in Normal Subjects and in Patients with Borderline Essential Hypertension (n = 50)

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</tbody>
</table>
high shear rates used in these experiments (≥ 52 sec⁻¹) were chosen for their approximation of those found in the precapillary vessels of normal subjects. At these shear rates, relative blood viscosity was either not significantly different (at 208 sec⁻¹) or only slightly higher (at 104 and 52 sec⁻¹) in patients with borderline hypertension (table 4). This finding, in agreement with previous studies in untreated patients with established essential hypertension, suggests that in borderline hypertensives the elevated plasma viscosity contributes significantly to the increased whole blood viscosity at high shear rates.

At intermediate (5.2 sec⁻¹) and low (≤ 0.5 sec⁻¹) shear rates, relative blood viscosity is an index of the degree of red cell aggregation. As shown in table 4, relative blood viscosity was progressively greater in patients with borderline hypertension. The magnitude of this elevation was inversely related to shear rate. Thus, at the intermediate shear rate of 5.2 sec⁻¹, relative blood viscosity was approximately 10.7% greater in hypertensive patients, while at a lower shear rate (0.5 sec⁻¹), the difference was 18.3%. These findings indicate that red cell aggregation is increased in patients with borderline hypertension.

Plasma viscosity was elevated in borderline hypertensive patients due to the elevated plasma protein concentrations. Although Tibblin and his coworkers found serum protein concentrations to be equivalent in normal and mildly hypertensive patients with similar hematocrits, blood viscosity was higher in their hypertensive subjects as well. This finding implies that fibrinogen concentration was higher in their hypertensive subjects and may have accounted, in large measure, for the elevated blood viscosities. Previous studies from this laboratory have shown that, in comparison to normal subjects, fibrinogen concentration in 49 patients with established essential hypertension was increased in 49 patients with established essential hypertension. To more precisely identify the role of elevated fibrinogen concentration in patients with established essential hypertension, 25 normal subjects and 25 patients with similar hematocrit levels were selected from a larger group. Blood viscosity remained elevated in the patients with established hypertension, largely because of the rheologic effects of increased fibrinogen concentration on plasma viscosity and red cell aggregation. Since fibrinogen concentration is the most powerful rheologic determinant of both plasma viscosity and the degree of red cell aggregation, the results of the current study also suggest that the hyperfibrinogenemia in borderline hypertension is an important etiologic factor determining the elevated blood viscosity.

The influence of fibrinogen concentration on plasma viscosity was found to be greater than that of the globulins. When the globulin fractions were considered individually, the beta globulin concentrations were the most influential. Since the beta-1 and beta-2 globulin concentrations were similar in these normal and borderline hypertensive subjects, it is likely that the elevated fibrinogen concentration alone accounted for the elevated plasma viscosity in the borderline hypertensive patients. These findings are in accord with previous studies in both humans and experimental animals.

In 1930, Harris and McLoughlin used a capillary viscometer to study the blood viscosity in 49 hypertensive patients and 21 normal subjects. They concluded that: "In the majority of cases of high blood pressure, the viscosity of the blood is higher than normal." Although they did not precisely define the pathophysiologic basis for it, their data show a highly significant correlation between systolic blood pressure and blood viscosity ($r = 0.73$, $p < 0.001$). Previously published reports from this laboratory have confirmed and expanded the findings of these early investigations.

The results of the current study show that blood pressures are quantitatively related to blood viscosity in normal subjects and in untreated patients with borderline essential hypertension. Furthermore, these studies show that the correlation of blood viscosity with systolic and diastolic blood pressures exists over a wide range of blood flow conditions (208 to 0.01 sec⁻¹), and that the rheologic basis for these correlations is shear rate dependent. Thus, only whole blood viscosity alone correlated with the systolic and diastolic blood pressures at the blood flow conditions present in the precapillary circulation (≥ 52 sec⁻¹). However, both whole blood and relative blood viscosities correlated with arterial pressures at the lower shear rates.

These findings suggest that, at the flow conditions present in the arterial circulation, elevated plasma viscosity is a primary contributing factor to the correlation between blood viscosity and blood pressures. At lower shear rates, plasma protein-mediated red cell aggregation becomes the major determinant of blood viscosity, and is responsible for the correlation of blood pressure with blood viscosity. To the extent that the plasma protein fractions determine plasma viscosity as well as the degree of red cell aggregation, this investigation suggests a need for additional studies that precisely define the physiologic or pathophysiologic role of plasma protein in blood pressure homeostasis.

The association of elevated blood viscosity and elevated blood pressure does not necessarily mean that the two are causally related. It may be that arteriolar vasoconstriction, by altering capillary hydrostatic forces and promoting hemoconcentration, may lead to elevated hematocrit and plasma protein concentrations and, thereby, the observed changes in blood viscosity. In the present study, however, the various protein fractions in borderline hypertensive patients do not change by the same degree. The fibrinogen concentration in borderline hypertension is elevated by 15% ($p < 0.05$), whereas this elevation is only 8% for total globulin concentration ($p < 0.05$) and 3% for albumin concentration ($p > 0.1$). The various globulin fractions also show different degrees of change. These results suggest a specific increase in certain globulin fractions and/or fibrinogen concentration in borderline hypertensive patients, rather than simple hemoconcentration.
Our studies show that even patients with marginal elevations of arterial pressure exhibit increased blood viscosity in direct proportion to the degree of blood pressure elevation. In addition, these studies demonstrate that the rheologic components producing the elevated blood viscosity vary with the conditions of blood flow. At higher shear rates, elevated plasma viscosity and hematocrit are responsible for the increased blood viscosity; at lower shear rates, increased red cell aggregation, which is a consequence of the elevated fibrinogen concentration in hypertensive patients, as well as increased plasma viscosity and hematocrit, are the basis for the elevated blood viscosity. To the extent that borderline hypertension represents an early developmental phase of essential hypertension, our results indicate that changes in the flow properties of blood are apparent even at this early phase of disordered arterial pressure regulation.

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