Mechanisms

Plasma Viscosity in Isolated Systolic Hypertension: The Role of Pulse Pressure

Giovanni Ciuffetti, Giuseppe Schillaci, Rita Lombardini, Matteo Pirro, Gaetano Vaudo, and Elmo Mannarino

Atherosclerosis is increasingly recognized as an inflammatory vascular disease, and high blood pressure (BP) has been suggested to exert a proinflammatory action. Whether plasma viscosity (PV), a major determinant of blood flow in microcirculation and a marker of systemic inflammation and cardiovascular risk, is increased in elderly subjects with isolated systolic hypertension is not known. In addition, the correlation of BP and its pulsatile component (ie, pulse pressure [PP]), with PV levels independent of the confounding effect of other cardiovascular risk factors has not been investigated. To this aim, we measured PV in 108 elderly men with never treated, uncomplicated isolated systolic hypertension, and in 60 healthy matched normotensive control subjects.

The PV values were higher in hypertensive subjects than in controls (1.39 ± 0.11 vs 1.34 ± 0.09 cP, P < .01). The PV showed a significant direct relation with both systolic BP (r = 0.32) and PP (r = 0.37, both P < .01), but not with diastolic BP (r = -0.03, P = .68). The PV was also directly associated with serum low-density lipoprotein cholesterol and triglycerides. In a multivariate analysis, PP was a significant predictor of PV levels when a consistent number of cardiovascular risk factors were simultaneously controlled for.

In conclusion, PV is elevated in elderly subjects with isolated systolic hypertension. Systolic BP and PP appear to be major determinants of PV levels in these patients, independent of the potential proinflammatory action of traditional cardiovascular risk factors. Am J Hypertens 2005;18:1005–1008 © 2005 American Journal of Hypertension, Ltd.

Key Words: Pulse pressure, isolated systolic hypertension, plasma viscosity, elderly.
Methods

Subjects

We enrolled 108 consecutive outpatients with never treated isolated hypertension, who were referred to the Angiology Section of the Department of Clinical and Experimental Medicine, University of Perugia. Inclusion criteria were: 1) male sex; 2) >60 years of age; 3) isolated systolic hypertension (systolic BP ≥160 mm Hg and diastolic BP <90 mm Hg in three readings at 1-week intervals); 4) no clinically overt coronary, cerebrovascular, or peripheral artery disease; and 5) no evidence of hypertension-induced end organ damage as shown by carotid ultrasound scanning, 12-lead electrocardiogram, M-mode echocardiography, lower limb Doppler ultrasound scan, or proteinuria. Sixty age-matched normotensive healthy male controls (systolic BP <140 mm Hg and diastolic BP <80 mm Hg) were recruited from the general population, hospital staff, relatives of patients, and patients attending hospital for routine cataract surgery.

Exclusion criteria for hypertensive and control subjects were: 1) body mass index ≥30 kg/m²; 2) diabetes mellitus; 3) hyperlipemia (serum cholesterol levels ≥7.76 mmol/L or serum triglyceride concentration ≥3.35 mmol/L); 4) smoking ≥20 cigarettes daily; 5) recent infection or surgery; 6) alcohol consumption >75 g/d; and 7) any pharmacologic therapy. None of the 168 participants had clinical or laboratory evidence of inflammation in the month before starting the study. All subjects gave informed consent to inclusion in the study, which was approved by the Perugia University Ethics Committee.

Procedures

All subjects underwent a clinical and instrumental checkup that included measurement of body mass index and BP. Subjects were not allowed to drink coffee or to smoke for 4 h before BP readings. After 10 min of rest, BP was measured with a mercury sphygmomanometer (three readings at 1-min intervals) and the average of the three readings was recorded together with the heart rate. The PP was calculated as the difference between systolic and diastolic BPs. Total cholesterol, triglycerides, and HDL cholesterol were determined by enzymatic-colorimetric method (Dimension Autoanalyzer, DADE Inc., Newark, NJ); LDL cholesterol was calculated according to the Friedewald equation.

The PV was measured with a rotational viscometer (Rotovisco Haake RV 100/CV100, measuring system ZB30, by ENCO srl, Chirignago, Venice, Italy) at a temperature of 37°C and a shear rate of 300 sec⁻¹ according to the recommendation of the International Committee for Standardization in Haematology.

The PV determinations were done in triplicate. As quality control, measurements were compared daily with those of water. The coefficient of variation was 3.8%.

Statistical Analysis

The SPSS statistical package, release 11.0 (SPSS Inc., Chicago, IL), was used for all statistical analyses. Values are expressed as the mean ± standard deviation. P values < .05 were considered significant. Hypertensive and control subjects were compared using the unpaired t test or the Mann-Whitney U test as appropriate for continuous variables, and the χ² test for categorical variables. Bivariate relations between the variables were evaluated by Pearson’s correlation coefficients. Multiple linear regression analysis was performed with PV as the dependent variable and age, smoking status, body mass index, total cholesterol, HDL cholesterol, triglycerides, and PP as independent variables.

We hypothesized that for a two-sided significance of P < .01 with a power of 90% to determining a difference of approximately 0.4 SD, we would need to obtain data from 130 subjects.

Results

Table 1 shows details of the 108 men with isolated systolic hypertension and 60 normotensive healthy controls, who were matched for age, smoking status, and body mass index with the hypertensive patients. By selection, systolic BP and PP were significantly greater in the hypertensive group. Total

<table>
<thead>
<tr>
<th>Table 1. Clinical and biological characteristics of study participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensives N = 108</td>
</tr>
<tr>
<td>Age (y)</td>
</tr>
<tr>
<td>Smokers (%)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
</tr>
<tr>
<td>Plasma viscosity (cP)</td>
</tr>
</tbody>
</table>

BP = blood pressure; LDL = low-density lipoprotein; HDL = high-density lipoprotein.
and LDL cholesterol were significantly higher in the hypertensive subjects, and HDL cholesterol was lower. Also PV was significantly higher in hypertensive patients.

Among hypertensive patients, PV levels correlated significantly with systolic BP ($r = 0.31; P < .01$), as well as with PP ($r = 0.37; P < .001$). Fig. 1 illustrates the correlation between PV and PP ($r^2 = 0.14, P < .001$). Significant direct correlations were also found with total cholesterol ($r = 0.19; P < .05$) and triglycerides ($r = 0.25; P < .01$), and an inverse one with HDL cholesterol ($r = −0.31; P < .01$). No significant correlation was observed with diastolic BP ($r = −0.03; P = .68$), heart rate ($r = −0.06, P = .50$), or self-reported physical activity ($r = −0.09, P = .36$).

In a multiple linear regression analysis, we tested the independent determinants of PV in hypertensive patients. In a model that tested the effects of age, smoking status, body mass index, PP, total cholesterol, HDL cholesterol, and serum triglycerides, a high PP ($\beta = 0.37, P < .001$) and a low HDL cholesterol ($\beta = −0.19, P < .01$) were the only significant predictors of PV.

### Discussion

This study shows that PV is increased in elderly men with never-treated, uncomplicated isolated systolic hypertension. The higher PV levels were directly associated with systolic BP and PP, and were independent of the potential confounding effect of traditional cardiovascular risk factors. Thus, in hypertensive patients, systolic BP and PP were stronger determinants of PV levels than diastolic BP.

These data extend to a larger population the findings obtained in a smaller group of 23 patients with isolated systolic hypertension.

One possible mechanism of these associations is represented by subclinical inflammation. The PV, an overall marker of the rheologic properties of plasma, is associated to an increased inflammatory response. Recent studies have shown that plasma concentrations of several humoral markers of systemic inflammation are elevated in hypertensive patients. Our results suggest that the stress generated by blood flow during the systole may have a role in stimulating release into circulation of humoral markers of inflammation irrespective of the proinflammatory action of other cardiovascular risk factors. Therefore, it may be hypothesized that high systolic BP and PP, through imposition of an oscillatory shear regime to the vasculature, may activate a systemic inflammatory reaction or possibly enhance a pre-existing inflammatory status. Accordingly, increased systolic BP and PP are paralleled by increased speed of propagation of the arterial pressure wave accompanied by earlier return of the reflected waves, which superimposes to incident pressure waves during systole. This contributes to generate on oscillatory bidirectional shear stress on the arterial wall and an increased arterial wall circumferential stress. Interestingly, conditions of altered shear stress (ie, oscillatory and low shear stress) stimulate adhesion molecule expression and the release of proinflammatory cytokines. Therefore, increased systolic BP and PP might induce alterations in the mechanical forces on the artery wall, thus contributing to the activation of the inflammatory cascade. A further pathophysiologic basis to this hypothesis may come from a study by Hodis et al., who previously showed that acute hypertension after aortic coarctation rapidly increases arterial wall monocyte/macrophage cellular invasion.

Our findings provide additional evidence that hypertension and low-grade systemic inflammation coexist, thus giving further support to the hypothesis that inflammation may participate into mediation of the proatherosclerotic effects of isolated systolic hypertension. Hence, the independent association found in the present study between systolic BP, PP, and PV levels in newly diagnosed hypertensive elderly men adds a new potential door to the link between isolated systolic hypertension and cardiovascular disease.

Some additional issues deserve more discussion. First, PP increase with age could affect coronary outcomes through increased systolic BP and left ventricular afterload, and through diminished coronary perfusion secondarily to diastolic BP reduction. Thus PP elevation tightens the relation between cardiac systolic performance and myocardial perfusion. The increase in PV, secondary to elevated PP, should contribute to increase peripheral resistance and cardiac afterload, and to impair the energetic cost to the heart to maintain adequate cardiac output. Moreover, the increase in PV might impair tissue perfusion. In fact, PV directly determines blood flow at the microcirculation level and plasma hyperviscosity results in a deterioration of microcirculatory blood flow, in particular in poststenotic areas with low shear forces.

Second, PV is a biochemically composite variable, which is influenced by acute (and chronic) phase proteins, including α2- macroglobulin and large lipoproteins. There is evidence to suggest that hepatic synthesis of fibrinogen is triggered by various mediators involved in the early

![FIG. 1. Scatter plot showing a direct correlation between pulse pressure and plasma viscosity in 108 patients with isolated systolic hypertension.](https://academic.oup.com/ajh/article-abstract/18/7/1005/220391/FIG.1)
stages of atherogenesis and in its clinical complications. In particular, the production and secretion of interleukin-6, the major cytokine of the acute phase response, is stimulated by damaged endothelial cells, fibroblasts, and activated monocytes and macrophages. Therefore, the increase in PV may be an easily accessible marker of early atherosclerosis. It could serve as a new parameter identifying those individuals at risk for major cardiovascular complications. It remains to be clarified whether its predictive power is any better or worse than the measurement of any single acute phase protein.

In conclusion, this is the first report showing that PV levels are increased in elderly men with newly diagnosed isolated systolic hypertension, independent of the potential proinflammatory action of traditional risk factors. Our results are also consistent with the hypothesis that systolic BP and PP are major determinants of the increased levels of PV observed in these subjects. Hence, by virtue of their potential to promote a proinflammatory state, elevated systolic BP and PP might act synergistically with increased PV levels in determining increased cardiovascular risk in elderly hypertensive men.

References