Association of Blood Pressure With Blood Viscosity in American Indians
The Strong Heart Study

Giovanni de Simone, Richard B. Devereux, Marcello Chinali, Lyle G. Best, Elisa T. Lee, Thomas K. Welty; for the Strong Heart Study Investigators

Abstract—Abnormalities in whole blood viscosity (WBV) have been implicated in hypertension. This study analyzes relations between WBV and blood pressure in the Strong Heart Study population of American Indians. We examined 676 participants (489 women, age 62±7 years) without prevalent cardiovascular disease or use of antihypertensive medications, digoxin, or aspirin. WBV was calculated from hematocrit and plasma protein concentration, at a shear rate of 208 seconds⁻¹, by a validated equation. Forty eight percent of participants were obese, 43% had diabetes, 19% had hypertension, and 30% were current smokers. WBV was higher in men, smokers, and participants with central obesity, but it was not associated with hypertension or diabetes, even accounting for confounders. After adjusting for gender, age, center, smoking, obesity, diabetes, and plasma creatinine, WBV was negatively related to pulse pressure (β=−0.13; P<0.001) and systolic pressure (β=−0.09; P<0.02), mainly because of negative relations with hematocrit (β=−0.11 and −0.10). Among hypertensive individuals, pulse pressure was positively related to age, diabetes, and female gender but not to WBV (multiple R=0.63; P<0.0001); in contrast, in normotensive individuals, pulse pressure was related negatively to WBV or hematocrit, independent of body mass index, without relation to diabetes (R=0.42; P<0.0001). Thus, under normal physiological conditions, in vivo WBV is negatively related pulse pressure. In contrast, the presence of arterial hypertension makes this relation less evident. (Hypertension. 2005;45:625-630.)

Key Words: blood volume ■ hematocrit ■ hypertension ■ pulse ■ risk factors

Abnormalities in blood viscosity have been implicated in a number of cardiovascular diseases.¹⁻³ Given the direct role of whole blood viscosity (WBV) in determining vascular resistance, recognized by Poiseuille,⁴ there is interest in possible relations between viscosity and hypertension.⁵⁻¹¹ A study performed in normotensive subjects⁶ demonstrated an independent association of WBV with diastolic or mean blood pressure, but not with systolic pressure, giving support to further research to investigate possible relations of WBV with hypertension and other cardiovascular risk factors. However, most mechanisms remain unclear.¹⁰ Unfortunately, direct determination of in vitro WBV is technically demanding and difficult to apply in epidemiological studies. We have previously shown that up to 83% of variability of WBV could be explained by microhematocrit and total plasma protein concentration (as a surrogate of plasma viscosity) over a range of shear rates from 0.1 to 208 seconds⁻¹.⁶

Relations between blood pressure and rheological components or WBV have rarely been studied in general populations.¹²⁻¹³ The Strong Heart Study is a population-based longitudinal survey in American Indians, an ethnic group with higher prevalence of obesity and diabetes than in previous studies on WBV, which provides an opportunity to investigate cross-sectional associations between blood pressure and estimated WBV in the presence of these increasingly prevalent cardiovascular risk factors, without confounding by medication effect or consequences of overt cardiovascular disease. For simplicity, the study has been performed only considering viscosity at a shear rate of 208 seconds⁻¹, approximating the shear stress in arterial and arteriolar circulation.

Methods

Population

The Strong Heart Study is a population-based longitudinal survey of cardiovascular risk factors and disease in American Indians from 3 communities in Arizona, 7 in Southwestern Oklahoma, and 3 in South and North Dakota, as previously reported.¹⁴⁻¹⁶ The phase 3 examination was conducted in 1998 to 1999 and included hematocrit and plasma protein determinations, not performed during phase 1 or 2, in 3680 participants, with 1793 hypertensive subjects and 1887...
normotensive subjects. Among these participants, 2491 (67%) were using cardioactive medications, including diuretics, β-blockers, angiotensin-converting enzyme inhibitors, Ca-channel blockers, other antihypertensive drugs, digoxin, or aspirin and were excluded from this study. Among the remaining subjects, 513 with prevalent cardiovascular disease (including adjudicated coronary heart disease, congestive heart failure, valve disease, and cerebrovascular or peripheral vascular disease) at the time of this evaluation were also excluded. A total of 676 participants, including obese and diabetic individuals, were finally selected (489 women, aged 62±7 years), 188 from Arizona, 249 from Oklahoma, and 239 from North/South Dakota.

Obesity and central fat distribution were defined by National Institutes of Health guidelines.19 Diabetes was identified by American Diabetes Association criteria.20 Diagnosis of untreated hypertension was based on measured blood pressure ≥140 mm Hg systolic and/or ≥90 mm Hg diastolic. Seated blood pressure was measured 3 times during the clinic visit, over a period of ~10 minutes, according to standardized procedures used for the study.

Methods
Fasting plasma glucose and insulin, as well as other blood tests, were measured by standard methods.16

WBV was determined in centipoises (cP) at a shear rate of 208 seconds−1, using the following equation:6

\[ \text{WBV} = 0.12 \times \text{hematocrit} (%) + 0.17 \times \text{plasma proteins (g/L)} \]

This equation has been validated by comparison with direct WBV measurements (r=0.92, n=50) in white and black adults, but not in American Indians, and by demonstrating that the degree of error introduced by the predictive equation is less than the year-to-year variability of directly measured WBV.6 This method has already been used for population-studies.21

Statistical Analysis
Data were analyzed using SPSS 11.0 software (SPSS, Chicago, Ill). Data are expressed as mean±SD. Descriptive statistics were obtained using standard normal or χ² distributions (with Monte Carlo method for computation of exact 2-tailed α-value, when appropriate). In hypotheses-testing analyses, the 3 field centers, Arizona, South and North Dakota, and Oklahoma, were represented by indicator variables. Relations between blood pressure and WBV or its principal determinant, hematocrit, were studied using ANCOVA and multiple linear regression analysis by enter or step-wise procedures and tolerance tests to allow only models with low degrees of collinearity (tolerance >0.70). The null hypothesis was rejected at 2-tailed P<0.05.

Results
Participant Characteristics
Diabetes, obesity, and central fat distribution were significantly more prevalent in Arizona (59%, 68%, and 86%, respectively) than in North/South Dakota (33%, 33%, and 71%) and Oklahoma (40%, 48%, and 73%; all P<0.001). In contrast, smoking was more frequent in North/South Dakota (43%) than in Arizona (15%) or Oklahoma (30%; P<0.0001).

Among participants, 324 (48%) were obese, 233 (35%) were overweight, and 514 (76%; 418 women) had central fat distribution, based on National Institutes of Health partition values for waist girth. Diabetes was found in 288 (43%; 214 women) and untreated hypertension in 128 (19%; 88 women); 205 participants (135 women) were current smokers and 222 (145 women) were former smokers.

Blood pressure was 149/82±12/11 mm Hg in hypertensive as opposed to 120/71±11/8 mm Hg in normotensive participants. Only 31 hypertensive persons (24%) had diastolic blood pressure ≥90 mm Hg, and only 6 (5%) had diastolic pressure ≥100 mm Hg. Thus, untreated arterial hypertension in this population sample was mainly isolated systolic; diastolic hypertension, when present, was mild. Hypertensive participants were similar in age (63±7 versus 62±7 years) and had slightly higher body mass index (32±6 versus 30±7 kg/m²; P=0.06) compared with normotensive participants.

Correlates of WBV
Hematocrit and WBV were higher in men and in the presence of obesity, central fat distribution, and current smoking, whereas no differences were found between hypertensive and normotensive or diabetic and nondiabetic participants (Table 1). Plasma protein concentration was also higher in men than in women (Table 1).

Hematocrit and WBV were higher in Oklahoma than in the other centers, whereas plasma protein concentration was slightly higher in the Dakotas, both in men and women. These differences were maintained after controlling for age and presence of diabetes (all, 0.01<P<0.004; Table 2).

After adjusting for gender, age, center, smoking status, presence of obesity, diabetes, and plasma creatinine (as a raw measure of renal function), systolic blood pressure was negatively related to WBV (P<0.01; Table 3, top panel), and hematocrit (β=−0.10; P<0.02), whereas no relation was found with diastolic blood pressure (Table 3, middle panel). Lower WBV was more strongly related to higher pulse pressure (P<0.003), independent of other significant associations, including older age, greater body mass index, female
hyperviscosity, 5,7,8,10,22 but it is not clear if this is a cause or effect.

The relations between WBV and blood pressure have been assessed in several studies, either in the absence or in the presence of arterial hypertension. 5,7,8,10,22 In most clinical patient populations, hypertension is associated with relative hyperviscosity, 5,7,8,10,22 but it is not clear if this is a cause or effect of high blood pressure, 9,23 or how previous treatment affects this relation. 9,11

In addition to being part of vascular resistance that thereby directly influences arterial pressure, higher WBV might also be a consequence of high blood pressure caused by increased filtration pressure, leading to hemoconcentration 24–26 or to direct deterioration of rheological variables. 23 Of note, Tarazi et al. 25 reported that increased hematocrit, a major cause of elevated WBV, occurred primarily at diastolic pressures ≥105 mm Hg. A more recent hypothesis is that high WBV and hypertension are not directly linked but instead share inciting genetic and/or environmental factors, including obesity, physical inactivity, and cigarette smoking. 11

In apparent contrast with previous reports, 27 the present study found that arterial hypertension was not associated with WBV estimated using a regression equation including both hematocrit and total plasma proteins 6 or with measured hematocrit. A weak negative association was found between WBV and systolic pressure, similar to our findings in normal individuals, 6 which was consistent with the predominance of normotensive subjects (4.45±0.58 cP in men and 4.05±0.45 cP in women). Similarly, hematocrit was comparable in hypertensive and normotensive participants of both genders (all P>0.1).

Pulse pressure, the component of blood pressure most related to WBV in this population, was examined separately in hypertensive and normotensive participants, using WBV and covariates, in stepwise regression model (Table 4). In individuals with arterial hypertension, pulse pressure was higher in Oklahoma and diabetic participants, and was directly related to age and female gender. In contrast, in normotensive individuals, pulse pressure was not influenced by diabetes but was related to higher body mass index and lower WBV. Similar relations were found with hematocrit (data not shown).

We have repeated the analyses shown in this study replacing WBV with hematocrit, a directly measured variable, and found the same results as with WBV (online Tables, see http://hyper.ahajournals.org).

**Discussion**

The relations between WBV and blood pressure have been assessed in several studies, either in the absence or in the presence of arterial hypertension. 5,7,8,10,22 In most clinical patient populations, hypertension is associated with relative hyperviscosity, 5,7,8,10,22 but it is not clear if this is a cause or effect of high blood pressure, 9,23 or how previous treatment affects this relation. 9,11

In addition to being part of vascular resistance that thereby directly influences arterial pressure, higher WBV might also influence this relation is masked. There are at least 2 possible reasons for this difference from normal. First, pressure natriuresis in untreated hypertensive adults can counterbalance the negative pulse pressure–WBV relation found in normotensive individuals. Second, when the cardiovascular system is more compromised, as in the presence of combined high blood pressure, obesity, and diabetes, pulse pressure is likely to be more influenced by the pressure burden imposed on the arterial tree and the arterial stiffness thereof. The differing results in the Oklahoma participants also suggests a genetic influence or an effect of unmeasured environmental variables.

**Table 2.** Difference in Estimated Whole Blood Viscosity and Its Components Among Field Centers

<table>
<thead>
<tr>
<th>Centers</th>
<th>Variables</th>
<th>Men (n=187)</th>
<th>Women (n=489)</th>
<th>Total (n=676)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arizona</td>
<td>WBV, cP at 208 sec⁻¹</td>
<td>4.36±0.58</td>
<td>4.01±0.48</td>
<td>4.11±0.53</td>
</tr>
<tr>
<td></td>
<td>Hematocrit, %</td>
<td>43.4±5.02</td>
<td>40.75±3.76</td>
<td>41.49±4.30</td>
</tr>
<tr>
<td></td>
<td>Plasma proteins, g/dL*</td>
<td>7.16±0.45</td>
<td>7.00±0.53</td>
<td>7.04±0.52</td>
</tr>
<tr>
<td>Dakotas</td>
<td>WBV, cP at 208 sec⁻¹</td>
<td>4.37±0.60</td>
<td>4.01±0.46</td>
<td>4.10±0.52</td>
</tr>
<tr>
<td></td>
<td>Hematocrit, %</td>
<td>43.23±4.91</td>
<td>40.49±3.64</td>
<td>41.22±4.18</td>
</tr>
<tr>
<td></td>
<td>Plasma proteins, g/dL*</td>
<td>7.37±0.55</td>
<td>7.15±0.59</td>
<td>7.21±0.58</td>
</tr>
<tr>
<td>Oklahoma</td>
<td>WBV, cP at 208 sec⁻¹</td>
<td>4.55±0.46</td>
<td>4.11±0.43</td>
<td>4.23±0.48</td>
</tr>
<tr>
<td></td>
<td>Hematocrit, %</td>
<td>45.05±3.68</td>
<td>41.37±3.46</td>
<td>42.41±3.89</td>
</tr>
<tr>
<td></td>
<td>Plasma proteins, g/dL*</td>
<td>7.13±0.48</td>
<td>7.12±0.44</td>
<td>7.12±0.45</td>
</tr>
</tbody>
</table>

*P<0.01 vs the other centers.

Raw means are shown but comparison is adjusted for age and presence of diabetes.
There are many potential reasons for the apparent inconsistency with previous clinical reports of a direct relation between arterial hypertension and increased WBV. One aspect, already mentioned, is that the hypertensive group was selected on the basis of absence of antihypertensive treatment and of overt cardiovascular disease. The hypertension of this untreated group of subjects was substantially systolic, a condition known to be associated with increased arterial stiffness. Previous studies used mainly diastolic pressure to diagnose hypertension (ie, a measure mostly related to increased peripheral resistance and therefore expected to be related to higher WBV and hematocrit). The hypertensive group in the present study had only relatively mild hypertension, probably without substantial modifications of renal hemodynamics. A recent investigation in a population sample of unselected hypertensive patients found a clear positive relationship between hypertension and blood viscosity, but their average diastolic blood pressure was substantially higher (93 mm Hg) than in the present population (82 mm Hg), suggesting that pressure-dependent hyperfiltration might have influenced this relation.

Another important aspect is that our hypertensive subjects were untreated, whereas many participants in most previous clinical studies received antihypertensive therapy. Antihypertensive therapy may affect blood viscosity by: (1) inducing diuresis and causing hemoconcentration (diuretics were the most used antihypertensive agents at the time of data collection of many studies); and (2) directly influencing red blood cell filterability. Antihypertensive treatment has been shown to decrease both WBV and blood pressure, indepen-
The main limitation of this study is that WBV was not directly measured and the equation used in this study is validated in an ethnically different population. Erythrocyte aggregability and impaired erythrocyte deformability may influence the magnitude of WBV,32,39,40 as may other less-studied components.13 Increased red blood cell aggregability and shear resistance of red blood cell aggregates have been proposed to play a role in the development of cardiovascular complications in hypertension.8 However, the effect of plasma protein concentration (which determines plasma viscosity) and, especially, hematocrit on WBV are much stronger than red blood cell aggregability and deformability.6 Because the effect of hematocrit in this study paralleled that of WBV, it is unlikely that a significant ethnical bias could have occurred. The balance among rheological components may also be disturbed by other unmeasured factors.10 This cross-sectional study also cannot assess WBV or hematocrit variation within individuals because of physiological and seasonal factors. Whether this time-related imprecision might have influenced results cannot be determined from the present data.

Finally, in this population sample, most participants were women with abdominal fat distribution, whereas intra-abdominal fat is related to blood pressure but is found predominantly in men.41 Thus, despite the results in multiple linear regression analysis, this sex distribution and prevalence of central obesity should be taken into account when interpreting these results.

**Perspectives**

This study suggests that the interrelations between WBV and blood pressure levels are complex. Future research on rheological and structural components of peripheral resistance in different ethnic groups and in the setting of never-treated hypertensive subjects with either diastolic or systolic hypertension might help clarifying whether WBV and/or hematocrit should be considered cofactors of altered peripheral resistance or markers of circulating volume status and the extent to which renal hemodynamic influence this relation in the presence of high blood pressure.

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**References**

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