Influence of serological factors and BMI on the blood pressure/hematocrit association in healthy young men and women

Abstract: The association between mean arterial blood pressure (MAP) and hematocrit (Hct) as a surrogate for blood viscosity was investigated in a young (average 20.0±2.3 years), healthy population of 174 men and 442 women. Health status was assessed by clinical examination and serological evaluation. Individuals with severe anemia or hemoconcentration, prior traumas or major surgical intervention, smokers, and pregnant or lactating women were excluded from the study. The MAP/Hct association was positive and significant (P=0.04) for women and negative, albeit not significantly so, for men. The MAP/Hct association was also evaluated in subgroups of the same population with a progressive step-by-step exclusion of: individuals with cholesterol >200 mg/dL; triglycerides >200 mg/dL; body mass index >25 kg/m²; and glucose >100 mg/dL. This consecutively reduced the strength of the positive MAP/Hct association in women, which became negative – although not significantly so – when all anomalously high factors were excluded. The same trend was found in men. Our study indicates that previously reported positive trends in the relationship between the MAP and Hct in the population are not present in a young, healthy population of men or women that excludes individuals with the confounding factors of above normal serological values and BMI.

Keywords: blood pressure, blood viscosity, hematocrit, vascular resistance, endothelial dysfunction

Introduction

A direct relationship between hypertension, elevated hematocrit (Hct), and blood viscosity was found in studies pioneered by Letcher et al.1 These results were confirmed by findings of the Edinburgh Artery Study, a study that evaluated the blood pressure/viscosity association in 1,592 men and women aged 55–74 years.2 This study concluded that there was evidence of a strong association between blood viscosity and arterial pressure, independently of confounding factors. The same conclusion was reached by the Gubbio Population Study (2,809 men and women aged 25–74 years).3 That study reported a significant independent association between Hct and the prevalence of hypertension and a positive relationship between Hct and blood pressure.

Studies conducted in a population4 of >100,000 blood donors in the Netherlands reported a positive association between hemoglobin levels and systolic and diastolic blood pressure in adult men and women (49.3±12.5 and 42.4±13.7 years). This study included individuals considered to be healthy with data adjusted for age, body mass index (BMI), mean daily temperature, season, smoking, and antihypertensive drug treatment.

However, studies in populations that can be clinically evaluated tend to show that a significant positive association between MAP and Hct is related to age and/or clinical factors that are not present in a young, healthy population of men or women that excludes individuals with the confounding factors of above normal serological values and BMI.
All participants were asked to provide their clinical history. Height, weight, BMI, and blood pressure (criteria of the VII Joint National Committee on Prevention, Detection, and Treatment; High Blood Pressure, National Heart, Lung, and Blood Institute; 2003) were measured at this time.

Hematocrit varies through the day as a function of fluid and food intake, level of exercise, etc. Therefore, to ensure a degree of uniformity of hydration, participants were summoned at 8 am for blood sampling, after 8–12 hours of fasting. Blood pressure was measured first after 5 minutes of resting in the sitting position with an automatic instrument (Omron model BP742, Omron Healthcare, Inc., Bannockburn, IL, USA) three times in the left arm at heart level, at 5-minute intervals and averaged. Glucose, cholesterol, and triglycerides were measured in drawn blood samples with the instrument Accutrend® GCT (Roche Diagnostics GmbH, Mannheim, Germany), which uses a drop of blood obtained from an index finger puncture. Hematocrit and hemoglobin determinations were made by the same method using the instrument HemoCue Hb 201 (HemoCue, Inc., Cypress, CA, USA). These tests were subsequently repeated for individuals who had significant clinical alterations, using standard laboratory analysis techniques.

**Statistical analysis**

The association between MAP and Hct for the population was evaluated by determining the Spearman’s correlation coefficient of these two variables. The influence of serological factors and BMI upon the MAP/Hct relationship was assessed by the consecutive step-by-step removal of individuals who had values above the normal thresholds for these parameters and reanalyzing the level of association by means of the Spearman’s correlation coefficient, excluding individuals according to the backward-stepwise selection method.11

The order of removal was established by ranking the serological parameters and the BMI above the normal threshold that caused the steepest slope on the MAP/Hct association (ie, produced the strongest effect) when only the individuals with this parameter anomaly were investigated. Individuals with the parameter showing the strongest effect were removed first. Statistical analysis was performed using the GraphPad Prism 5 software (GraphPad Software, Inc., La Jolla, CA, USA). Differences were considered significant when \( P<0.05 \).

**Results**

The study included 616 individuals (442 women and 174 men), aged 17–25 years. The average age was 20.0±2.3 years. The principal characteristics of the population studied are given in Table 1.
Table 1 Demographic, anthropometric, and serologic characteristics of the young adult population examined in the municipality of the city of Durango, Mexico

<table>
<thead>
<tr>
<th>Sex</th>
<th>Men =174</th>
<th>Women =442</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>20.4±2.5</td>
<td>19.7±2.2</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>75.8±15.3</td>
<td>60.1±11.8</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.74±0.07</td>
<td>1.60±0.06</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.8±4.3</td>
<td>23.4±3.2</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>91.2±7.4</td>
<td>85.0±8.3</td>
</tr>
<tr>
<td>Cardiac frequency, beats/minute</td>
<td>67.2±11.5</td>
<td>71.0±11.7</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.94±0.06</td>
<td>0.89±0.06</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>22.9±6.5</td>
<td>28.1±8.3</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>48.2±3.2</td>
<td>43.1±2.8</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>163.7±17.4</td>
<td>162.7±16.8*</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>97.4±18.5</td>
<td>95.4±15.1*</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>150.7±98.0</td>
<td>142.9±85.0*</td>
</tr>
</tbody>
</table>

Notes: All demographic and anthropometric parameters, including Hct, are significantly different (P<0.002). Serological parameters (*) are not significantly different.

Abbreviations: BMI; body mass index; nr, normal range; Hct, hematocrit.

The relationship between MAP and Hct was evaluated for the whole study population separated by sex. Results are presented in Figure 1 showing that the trend of MAP/Hct association is positive and significant for women (P=0.04; r=0.10), and negative – albeit not significant – for men (P=0.91; r=0.05).

As shown in Table 1, men and women presented variability in parameter values. Some individuals exceeded the normal serological and BMI thresholds. The differences between and men and women in BMI, MAP, glucose, cholesterol, and triglycerides are typical of the Mexican population; these same trends have been previously reported. The difference in Hct between men and women is found in all healthy young populations.

The slope of the MAP/Hct association was evaluated for groups whose individuals had each of their serological and BMI values above the normalcy threshold. This analysis showed that the steepest slope for the MAP/Hct relationship occurred in individuals with cholesterol levels >200 mg/dL; progressively lesser effects were observed in the order of parameters shown in Table 2.

This information was used to reevaluate the MAP/Hct relationship in groups in which individuals with values above the threshold for a given parameter were progressively removed from the respective group, in the order shown in Table 2, obtaining the results shown in Tables 3 and 4.

The net effect of this treatment of the data was the non-significant lowering of the value of m (slope) (Tables 3 and 4) in the association between MAP and Hct. Excluding women with abnormally high cholesterol caused their positive MAP/Hct association to become not statistically significant, changing the P-value from 0.04–0.14. The subsequent exclusion of women with high triglycerides yielded P=0.90 for the MAP/Hct association. Further step-by-step removal of individuals with above threshold values of BMI and glucose caused the trend to become negative (but not significant). Applying the procedure to the data from men caused the negative slope of

Figure 1 MAP plotted as function of Hct for the study population of individuals described in Table 1.

Notes: The association MAP/Hct is positive and significant (P=0.04; r=0.10) for women (n=442) and negative but not significant (r=0.05) for men (n=174). This association becomes negative but not significant for women when individuals with serological and BMI values exceeding normal values are excluded. The same exclusion applied to men causes the association to become more negative without reaching significance.

Abbreviations: MAP, mean arterial blood pressure; Hct, hematocrit; BMI, body mass index; n, number.
Table 2 Thresholds defining the upper limit of parameters for the normal population

<table>
<thead>
<tr>
<th>Thresholds</th>
<th>Average and STD of % exceeding threshold</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 mg/dL</td>
<td>223.4±22.8; 4.0%</td>
<td>219.3±20.4; 4.1%</td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>300.2±109.5; 21.3%</td>
<td>297.9±108.6; 15.4%</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 kg/m²</td>
<td>27.9±3.2; 46.6%</td>
<td>28.5±3.5; 28.7%</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td>113.7±15.0; 39.1%</td>
<td>110.0±10.0; 36.0%</td>
</tr>
</tbody>
</table>

Abbreviations: STD, standard deviation; BMI, body mass index.

Table 3 Women

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>m, mmHg/Hct P</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women</td>
<td>442</td>
<td>0.285±0.140</td>
<td>0.04</td>
</tr>
<tr>
<td>All minus chol &gt;200 mg/dL</td>
<td>424</td>
<td>0.214±0.145</td>
<td>ns</td>
</tr>
<tr>
<td>All minus chol, trig &gt;200 mg/dL</td>
<td>363</td>
<td>0.020±0.156</td>
<td>ns</td>
</tr>
<tr>
<td>All minus chol, trig</td>
<td>266</td>
<td>-0.022±0.178</td>
<td>ns</td>
</tr>
<tr>
<td>BMI &gt;25 kg/m²</td>
<td>166</td>
<td>-0.032±0.213</td>
<td>ns</td>
</tr>
<tr>
<td>All minus chol, trig, BMI, glu &gt;100 mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: Statistical characteristics of the association MAP versus Hct as a function of threshold of chol, trig, BMI, and glu.
Abbreviations: MAP, mean arterial blood pressure; m, slope; Hct, hematocrit; chol, cholesterol; trig, triglycerides; BMI, body mass index; glu, glucose; ns, nonsignificant association; n, number.

Table 4 Men

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>m (slope) P</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>All men</td>
<td>174</td>
<td>-0.020±0.179</td>
<td>ns</td>
</tr>
<tr>
<td>All minus chol &gt;200 mg/dL</td>
<td>167</td>
<td>-0.024±0.185</td>
<td>ns</td>
</tr>
<tr>
<td>All minus chol, trig &gt;200 mg/dL</td>
<td>134</td>
<td>-0.035±0.206</td>
<td>ns</td>
</tr>
<tr>
<td>All minus chol, trig</td>
<td>77</td>
<td>-0.019±0.260</td>
<td>ns</td>
</tr>
<tr>
<td>BMI &gt;25 kg/m²</td>
<td>39</td>
<td>-0.193±0.368</td>
<td>ns</td>
</tr>
</tbody>
</table>

Notes: Statistical characteristics of the association MAP versus Hct as a function of threshold of chol, trig, BMI, and glu.
Abbreviations: m, slope; Hct, hematocrit; chol, cholesterol; trig, triglycerides; BMI, body mass index; glu, glucose; ns, nonsignificant association; n, number.

The path taken to investigate the effect of above threshold serological parameters and BMI on the MAP/Hct association is somewhat arbitrary since it does not account for the incidence of occurrence (ie, proportion of individuals) of the abnormalities in the population. The significant result is that there is no MAP/Hct association in a population that has normal serological data and BMI, and that – in the tested population – only 9% of women and 22% of men could be considered normal, according to the chosen criteria.

The proportion of males with no BMI or serology abnormalities was 28.7% versus 38.7% for women, a difference due to the incidence of overweight and obesity in men (46.6% versus 28.5%).

Blood viscosity is primarily determined by Hct, being a nonlinear function of this parameter.

However, the relationship between blood viscosity and Hct for the normal range of variability of Hct in the population can be considered linear, which facilitates the study of the MAP/blood viscosity relationship in large populations, where the measurement of blood viscosity could be substituted with the measurement of Hct.

In our study, we used Hct as a surrogate for blood viscosity, an assumption that may not be accurate in older individuals who may show altered plasma composition, particularly concerning fibrinogen and other rheological abnormalities, such as decreased red blood cell flexibility. Although we did not evaluate blood fibrinogen, this assumption should be accurate for the population studied, given its age and health.

Blood viscosity is one of the determinants of peripheral vascular resistance and, hence, in a circulatory system consisting of rigid tubes increasing blood viscosity increases vascular resistance, according to the Hagen–Poiseuille law. Supporting experimental data on the effect of blood viscosity on MAP originate with the classical studies of Richardson and Guyton and those of Messmer et al. However, the Hct...
changes studied were significantly greater than those associated with the variability of Hct in the normal population.

Experimental studies on changes of Hct in the range of variability of the normal population yield different results. Martini et al. showed in awake animals that acutely increasing blood viscosity above normal by about 10% through altering isovolemic hemocoencentration significantly lowered the MAP and increased the cardiac output. It should be noted that these are acute responses that may not extrapolate to chronic conditions. However, these changes of blood pressure lasting several hours do not appear to be regulated by baroreceptor responses.

The control of peripheral vascular resistance in the normal organism independently from the activity of the central nervous system is linked to mechanotransduction, via shear stress at the blood vessel wall that governs the production of vasodilators. Shear stress is in part determined by blood viscosity, which can have two opposing effects on peripheral vascular resistance. Namely, it can have a direct effect due to simple hemodynamic hindrance and a second, opposite effect due to the response to vasodilator release.

Evidence for lack of association between MAP and blood viscosity

Our results support the concept that increased Hct does not lead to an increased MAP in the young, healthy population. Furthermore, our present and previous studies indicate that the association may be negative, with increased Hct leading to lower MAP. Therefore, it is of interest to briefly analyze the results of previous studies in terms of the characteristics of the populations tested.

The relationship between blood viscosity and MAP was studied in a healthy population of 84 men and 65 women (30.6±8.0 years) from the city of Durango. The trend of association with MAP/viscosity was negative but not significant for women; there was a negative linear correlation (r=0.22; \(P=0.03\)) for men. The study of de Simone et al. found a significant relation between SBP, DBP, MAP, and blood viscosity (measured over a range of shear rates) as well as Hct (r=0.17–0.23; all \(P<0.05\)) in a cohort of normotensive members of the employed population in New York City. The study included apparently normal men and women who were 27–75 years old.

Adaptation to altitude increases Hct and MAP, the increase in MAP preceding the increase in Hct; however, the prolonged residence at high altitude lowers MAP relative to that of sea level residents. The decrease of MAP with altitude is attributed to the relaxation of the vascular smooth muscle, increased collateral circulation, increased vascularization, higher red blood cell and hemoglobin levels, hypocloric stress, and respiratory ailments. However, the hypothesis that this may be due to increased mechanotransduction caused by increased Hct and blood viscosity appears to have not been considered. In general, children and young adults of populations that adapt to altitude by increasing Hct have comparatively lower MAP than similarly aged populations at sea level.

A common trend in these studies is that the MAP/Hct association is positive in conditions where the organism has some form of dysfunction; it is not significant in healthy persons.

Conclusion

Our results show that, in normal healthy males and females, MAP is not elevated when Hct is higher than the norm if
the serological parameters and the BMI do not exceed the normalcy thresholds. Most studies in the literature that report a positive and significant association between MAP and Hct include older individuals. Values of plasma glucose, cholesterol, and triglycerides exceeding the normal threshold are related to increased blood pressure. Hence, it is not surprising that the exclusion of these individuals lowers the strength of the MAP/Hct association. A mechanism that may in part explain the lack of MAP/Hct association for normal individuals is the increase of shear stress at the blood vessel wall interface due to increased viscosity, which – according to the mechanisms of endothelial biochemical mechanotransduction – increases the release of vasodilators by the endothelium, an effect not present with endothelial dysfunction.8

Our results indicate that the increase in Hct in healthy young individuals is not related to the increase of MAP.

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Disclosure
The authors report no conflicts of interest in this work.

References