Is High Pulse Pressure a Marker of Preclinical Cardiovascular Disease?

Giovanni de Simone, Mary J. Roman, Michael H. Alderman, Maurizio Galderisi, Oreste de Divitiis, Richard B. Devereux

Abstract—This study tests the hypothesis that high brachial pulse pressure might constitute preclinical cardiovascular disease, rather than a risk factor. We studied 1250 subjects (472 nonobese normotensive [<135/80 mm Hg] and 778 untreated hypertensive). Central pulse pressure was estimated from brachial pulse pressure and age and divided by stroke volume (PP/SV). Brachial pulse pressure was considered high when >63 mm Hg, and peripheral resistance high when >90th percentile of normal distribution. Among hypertensive subjects, 34% had high resistance; among them, 33% had high brachial pulse pressure, as opposed to 147 of 516 patients (28.5%) with normal resistance ($P$=not significant). After adjusting for age, sex, race, body mass index, heart rate, and center, left ventricular (LV) internal dimension and mass were lower with high resistance, and higher when brachial pulse pressure was high. PP/SV was 36% higher with high resistance than with normal resistance, and higher when brachial pulse pressure was high (all $P$<0.0001). Factorial analysis demonstrated that associations of high brachial pulse pressure with both higher PP/SV and LV mass were independent of other pressure components. Thus, because of these associations, our hypothesis is that in hypertension, pulse pressure may be considered as a marker of preclinical cardiovascular disease, similar to LV mass and PP/SV, rather than a cardiovascular risk factor. (Hypertension. 2005;45:575-579.)

Key Words: hypertension, arterial | blood pressure | aging | atherosclerosis

Renewed interest in pulse pressure (PP) has heightened because of increasing evidence of its association with high cardiovascular risk.1-9 In relation to age, a wide PP may result from increased systolic blood pressure (BP), decreased diastolic BP, or both.8,9 High systolic pressure increases vascular load (a determinant of left ventricular (LV) geometry), whereas low diastolic pressure may reduce coronary perfusion pressure, both of which provide pathophysiologic explanations for the prognostic value of PP.10,11

Increased peripheral resistance reflects the enhanced obstacle to the blood flow opposed by arterioles and is the hallmark of arterial hypertension. In contrast, increased PP is a function of increased systolic ejection to distend conduit arteries and/or loss of the elasticity of arteries needed to accommodate ejected blood and restore arterial volume thereafter. Thus, in the natural progression of hypertension, increased PP might be consequence of atherosclerosis or arterial wall fibrosis and/or calcification and might be a marker of structural alterations of the conduit arteries. In this scenario, high PP may signify a condition more severe than elevated peripheral resistance.

Thus, in the time course of cardiovascular disease, high PP may indicate preclinical vascular disease, whereas arterial hypertension is the risk factor for the development of such preclinical disease.12 Accordingly, this study has been designed to test the hypothesis that high PP is a marker of “preclinical cardiovascular disease,”12 independent of the level of total peripheral resistance. If confirmed, this hypothesis might refine understanding of the clinical impact of high PP on cardiovascular risk and modify risk stratification.

Methods

From 2 centers, we studied 1504 adults without prevalent cardiovascular disease: 942 were Americans (474 hypertensive subjects from a worksite-based study and 468 normotensive volunteers) and 562 were Italians (306 hypertensive subjects seen in the outpatient clinic and 256 normotensive volunteers). Detailed characteristics of this composite study population have been previously reported.13-18 Hypertensive participants were under pharmacological wash-out (for at least 2 weeks) or previously untreated for arterial hypertension. Overweight and obesity were classified according to 1998 National Institutes of Health Guidelines.19 For the purpose of this study, we selected a nonobese control group (body mass index [BMI] <30 kg/m²) with normal BP (ie, <130/85 mm Hg),20 resulting in a study population of 1250 individuals, including the hypertensive participants.
The ratio of PP central to stroke volume (PP/SV) was therefore estimated from PPbrachial, using an age-adjusted equation, previously validated.27 Relative wall thickness was calculated as posterior wall thickness/LV internal radius. Stroke volume was generated from LV internal systolic and diastolic diameters using z-derived method to calculate volumes.23 Cardiac output and total peripheral resistance (TPR) were also computed by standard formulas.

Echocardiographic Methods
Echocardiograms were obtained using standardized acquisition methods used in multiple studies from the 2 echocardiography laboratories.17,18,21,22 Measurements were made as previously reported,17,18,21,22 from 2-dimensional targeted M-mode echo paper tracings according to the recommendations of the American Society of Echocardiography.23 LV mass was calculated by adjusted American Society of Echocardiography method24 and normalized for height.2,15 Relative wall thickness was calculated as posterior wall thickness/LV internal radius. Stroke volume was generated from LV internal systolic and diastolic diameters using z-derived method to calculate volumes.23 The ratio of PP central to stroke volume (PP/SV) was therefore computed as a marker of preclinical cardiovascular disease, which has been prognostically validated.27

Statistical Analysis
Data were analyzed using SPSS 12.0 software (SPSS, Chicago, Ill). Descriptive statistics were displayed as mean±1 standard deviation or χ² distributions (with Monte Carlo estimation of exact probability values). Distribution of TPR was obtained in the normal population and the 90th percentile was used to define a subgroup of hypertensive subjects with high peripheral resistance (>1988 dynes/sec per cm⁻²). TPR and PPbrachial were examined using 2-factor ANCOVA, adjusting for age, BMI, sex, race, heart rate, and country. Principal component analysis was used to assess whether PPbrachial was related to markers of preclinical cardiovascular disease independent of other pressure components.28

Factorial analysis with extraction of principal components was performed to analyze variance components among variables with high level of collinearity (age, BMI, heart rate, total peripheral resistance, PPbrachial, systolic and diastolic blood pressure). A correlation matrix method was used and factors with eigenvalues greater than 0.8 were identified. A scree plot was used to visualize whether the identified cutoff eigenvalues allowed the extraction of main factors (principal components) accounting for most of variance. For each observation and each extracted component, the component score was computed. The resulting component score variables, representative of the 7 variables used in the analysis, could be used, without any collinearity, in place of all original variables in multiple linear regression models with LV mass and PP/SV as dependent variables, with negligible loss of information. To assess multicollinearity, every covariate was related to all other covariates in the model and the coefficient of determination (r²) was computed. Tolerance was calculated as the reciprocal of the coefficient of determination (1−r²) of every independent variable, as a measure of unexplained variance. A tolerance >0.80 can be considered near optimal, as indicative of a level of collinearity that cannot remarkably affect stability of results.

Results
Table 1 summarizes characteristics of the study population. Hypertensive subjects were older and heavier than normotensive individuals, had higher mean heart rate, and included higher proportions of men, nonwhite, and overweight/obese individuals (Table 1).

Among hypertensive patients, 264 (34%) had high TPR, and among them 88 (33%) had also high PPbrachial, as opposed to 147 of 514 patients (28.5%) with normal TPR (P<0.15).

Table 2 shows that hypertensive patients with high TPR were older than those with normal TPR, and within these groups those with high PPbrachial were the oldest. BMI was lower in patients with high TPR, whereas no effect was found for high PPbrachial.

LV Geometry and PP/SV Ratio
The Figure shows that after adjusting for covariates, LV diastolic dimension and LV mass were lower in patients with high TPR than in those with normal TPR, and higher in those with high than with normal PPbrachial. Parallel results with

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**TABLE 1. Characteristics of Normotensive and Hypertensive Participants**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive (n=472)</th>
<th>Hypertensive (n=778)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>42.18±11.72</td>
<td>40.82±10.57*</td>
</tr>
<tr>
<td>BMI, kg/m</td>
<td>24.03±2.89</td>
<td>27.85±4.41*</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>67.45±11.00</td>
<td>70.75±11.41*</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>114.97±9.29</td>
<td>152.54±17.09</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>71.91±7.24</td>
<td>95.13±9.90</td>
</tr>
<tr>
<td>Gender, % women</td>
<td>46</td>
<td>36*</td>
</tr>
<tr>
<td>Nonwhite, %</td>
<td>23</td>
<td>34*</td>
</tr>
<tr>
<td>Overweight/obese, %</td>
<td>39/0</td>
<td>51/24*</td>
</tr>
</tbody>
</table>

*P<0.0001

**TABLE 2. Characteristics of Groups With Normal or High Pulse Pressure in Relation to Normal or High Peripheral Resistance**

<table>
<thead>
<tr>
<th>Hypertensive Subjects</th>
<th>Normal Controls (n=472)</th>
<th>Normal Peripheral Resistance (n=367)</th>
<th>High Peripheral Resistance (n=147)</th>
<th>Normal Peripheral Resistance (n=176)</th>
<th>High Peripheral Resistance (n=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>42.18±11.72</td>
<td>47.77±10.32</td>
<td>54.98±10.99</td>
<td>50.61±9.25</td>
<td>56.97±8.22†</td>
</tr>
<tr>
<td>BMI, kg/m</td>
<td>24.03±2.89</td>
<td>28.47±4.53</td>
<td>27.91±4.50</td>
<td>26.99±3.99</td>
<td>26.86±4.10‡</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>114.97±9.29</td>
<td>143.30±12.48</td>
<td>167.84±14.82</td>
<td>149.12±12.08</td>
<td>172.56±13.92</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>71.91±7.24</td>
<td>94.36±9.12</td>
<td>92.07±10.95</td>
<td>99.18±9.59</td>
<td>95.32±10.14</td>
</tr>
<tr>
<td>PP, mm Hg</td>
<td>43.06±7.59</td>
<td>48.87±8.79</td>
<td>75.76±11.50</td>
<td>49.94±9.28</td>
<td>77.24±10.93</td>
</tr>
<tr>
<td>Estimated central PP, mm Hg</td>
<td>43.31±5.33</td>
<td>48.09±5.11</td>
<td>58.46±6.01</td>
<td>49.52±4.86</td>
<td>59.64±4.98†</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure.

*P<0.0001 pulse pressure classification effect. †P<0.006; ‡P<0.0001 peripheral resistance classification effect.
similar statistical significance were observed for LV mass index in g/m². Relative wall thickness, the index of LV concentricity, was higher with high than with normal TPR, whereas there was no association with high PP_brachial.

The ratio PP/SV was substantially higher, by an average 36%, in subjects with high TPR than in those with normal TPR (Figure) and within groups with normal or high TPR, it was significantly higher when PP_brachial was high.

### Analyses Using Continuous Variables

To assess the interaction among all variables of interest, independent of predetermined cutoff points, multiple regression models were generated in the whole population (including normotensive and hypertensive subjects) to examine independent correlates of LV mass and PP/SV. Because of the high collinearity among potential independent correlates of these 2 markers of preclinical cardiovascular disease, factorial analysis was performed to extract principal components from primary predictors of both LV mass and PP/SV (age, BMI, heart rate, total peripheral resistance, PP_brachial, and systolic and diastolic BP). The estimates of the variance in each variable accounted for by the components, defined “communalities,” were between 0.83 and 0.97, with only age having a lower value (0.63), indicating that the extracted components represented the primary predictors well. Based on the predefined eigen value (0.8), 4 extracted components explained 86% of the variability of the original 7 predictors, with only a 14% loss of information.

### TABLE 3. Rotated Component Matrix of Principal Component Extraction, Performed on Age, BMI, Heart Rate, Total Peripheral Resistance, Brachial Pulse Pressure, and Systolic and Diastolic Blood Pressure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.752</td>
</tr>
<tr>
<td>BMI, kg/m</td>
<td>0.019</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>-0.035</td>
</tr>
<tr>
<td>Peripheral resistance, dynes/sec/cm²</td>
<td>0.119</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>0.890</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>0.679</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>0.163</td>
</tr>
</tbody>
</table>


### TABLE 4. Independent Correlates of LV Mass and PP/SV in Multiple Regression Models Using Principal Components of Variance of Age, BMI, Heart Rate, Total Peripheral Resistance, PP_brachial, and Systolic and Diastolic Blood Pressure

<table>
<thead>
<tr>
<th>Variable</th>
<th>LVM Independent Correlates</th>
<th>PP/SV Independent Correlates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Multiple R=0.66</td>
<td>Multiple R=0.67</td>
</tr>
<tr>
<td>(Constant)</td>
<td>212.52</td>
<td>0.60</td>
</tr>
<tr>
<td>Component 1</td>
<td>15.85†</td>
<td>0.30</td>
</tr>
<tr>
<td>Component 2</td>
<td>11.25†</td>
<td>0.21</td>
</tr>
<tr>
<td>Component 3</td>
<td>1.22</td>
<td>0.02</td>
</tr>
<tr>
<td>Component 4</td>
<td>19.11†</td>
<td>0.36</td>
</tr>
<tr>
<td>Female</td>
<td>-39.80†</td>
<td>-0.37</td>
</tr>
<tr>
<td>USA origin</td>
<td>5.00</td>
<td>0.05</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>4.04</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*P<0.04; †P<0.0001.
second component. The second component was most highly correlated with total peripheral resistance, systolic BP, and diastolic BP, but only diastolic BP showed weak correlations with the other 3 components. The third component was most highly correlated with heart rate and total peripheral resistance, but only heart rate well-represented this component, because it did not show correlations with other components. The fourth component was most highly correlated with BMI.

These component scores were used to model regression equations for LV mass and PP/SV, together with gender (1=male, 2=female), country (1=Italy, 2=US), and ethnicity (1=white, 2=nonwhite). As expected, the level of tolerance of regression models was excellent, because multicollinearity was eliminated (Table 4). Table 4 shows that LV mass was independently related to male gender and the first, second, and fourth components, but not with the third component (most representative of heart rate). In contrast, all components were independently related to PP/SV, with the strongest association with factors representative of aging, PP_brachial and diastolic BP. When a categorical variable indicating the presence or the absence of arterial hypertension was also included in the regression model, the results were substantially confirmed (not shown), but a collinearity was evident between hypertension status and the second component, most representative of diastolic BP.

**Discussion**

There is a large literature on PP, which is often identified as an independent cardiovascular risk factor. Inconsistent findings are found on whether this prognostic effect is related to systolic BP, a problem that is more relevant on epidemiological basis of both the resistance element and the pulsatile element of our analysis.

A brachial PP >63 mm Hg is associated with greater increases in both LV mass and a surrogate index of arterial stiffness, 2 potent and independent markers of preclinical cardiovascular disease independent of a number of physiological confounders, including level of peripheral resistance and other BP components, suggesting that high PP represents a sign of established cardiovascular damage in the setting of arterial hypertension. Accordingly, we suggest elevated brachial PP be considered a marker of established preclinical cardiovascular disease, rather than a risk factor for the development of arterial disease. Whether risk stratification can be improved, by considering PP as a marker of preclinical cardiovascular disease (and therefore to be added to the level.
of systolic/diastolic BP for risk stratification) ultimately needs to be proven, using more direct measures of arterial stiffness and prospective studies.

Acknowledgments

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References

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