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

R enewed 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.13-15 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.
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>50.82±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

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 height2.7,13 Relative wall thickness was calculated as posterior wall thickness/LV internal diameter, using age-adjusted equation, previously estimated from PPbrachial, using an age-adjusted equation, previously validated.27

Descriptive statistics were displayed as mean (brachial)P P

BP

BP was measured at the end of the echo examination. A brachial (brachial) PP>63 mm Hg was considered abnormal, because this value has been shown to predict adverse prognosis.26 Central (central) PP was estimated from PPbrachial using an age-adjusted equation, previously generated in 230 normotensive or hypertensive subjects:27

\[ \text{PP}_{\text{central}} = \text{PP}_{\text{brachial}} 	imes 0.49 + \text{age} \times 0.30 - 7.11 \]

The ratio of PP 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±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 (>0.988 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.26

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 of 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%) also had 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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal Controls (n=472)</th>
<th>Normal Peripheral Resistance</th>
<th>Hypertensive Subjects</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>
</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>
</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>
</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>
</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>
</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>
</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/m$^2$. 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.

The component matrix helped to determine what the components represented (Table 3). The first component was most highly correlated with age, PP$_{brachial}$, and systolic BP. However, age and PP$_{brachial}$ better represented this component than systolic BP, because they were less correlated with the other 3 components, whereas systolic BP was similarly represented in the

**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 1</th>
<th>Components 2</th>
<th>Components 3</th>
<th>Components 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>0.752</td>
<td>0.088</td>
<td>−0.214</td>
<td>−0.088</td>
</tr>
<tr>
<td>BMI, kg/m</td>
<td>0.019</td>
<td>0.089</td>
<td>0.030</td>
<td>0.982</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>−0.035</td>
<td>0.100</td>
<td>0.938</td>
<td>−0.013</td>
</tr>
<tr>
<td>Peripheral resistance, dynes × sec × cm$^{-5}$</td>
<td>0.119</td>
<td>0.639</td>
<td>−0.604</td>
<td>−0.196</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>0.890</td>
<td>0.164</td>
<td>0.079</td>
<td>0.083</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>0.679</td>
<td>0.683</td>
<td>0.101</td>
<td>0.142</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>0.163</td>
<td>0.926</td>
<td>0.080</td>
<td>0.141</td>
</tr>
</tbody>
</table>

Extraction method: principal component analysis.
Rotation method: Varimax with Kaiser normalization. Rotation converged in 5 iterations.

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.

The component matrix helped to determine what the components represented (Table 3). The first component was most highly correlated with age, PP$_{brachial}$, and systolic BP. However, age and PP$_{brachial}$ better represented this component than systolic BP, because they were less correlated with the other 3 components, whereas systolic BP was similarly represented in the

**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>Component Variables</th>
<th>LVM</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>b</td>
<td>β</td>
<td>Tolerance</td>
<td>b</td>
<td>β</td>
<td>Tolerance</td>
</tr>
<tr>
<td>(Constant)</td>
<td>212.52</td>
<td>0.60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Component 1</td>
<td>15.85</td>
<td>0.30</td>
<td>0.95</td>
<td>0.08</td>
<td>0.44</td>
</tr>
<tr>
<td>Component 2</td>
<td>11.25</td>
<td>0.21</td>
<td>0.93</td>
<td>0.06</td>
<td>0.32</td>
</tr>
<tr>
<td>Component 3</td>
<td>1.22</td>
<td>0.02</td>
<td>0.95</td>
<td>−0.03</td>
<td>−0.15</td>
</tr>
<tr>
<td>Component 4</td>
<td>19.11</td>
<td>0.36</td>
<td>0.99</td>
<td>−0.05</td>
<td>−0.30</td>
</tr>
<tr>
<td>Female</td>
<td>−39.80</td>
<td>0.37</td>
<td>0.95</td>
<td>0.09</td>
<td>0.25</td>
</tr>
<tr>
<td>USA origin</td>
<td>5.00</td>
<td>0.05</td>
<td>0.66</td>
<td>−0.02</td>
<td>−0.05</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>4.04</td>
<td>0.03</td>
<td>0.74</td>
<td>−0.01</td>
<td>−0.01</td>
</tr>
</tbody>
</table>

*$p<0.04$; †$p<0.0001$.  

LV diameter (upper left panel), mass (upper right panel), relative wall thickness (lower left panel), and pulse pressure to stroke volume ratio (PP/SV, lower right panel) in relation to magnitude of total peripheral resistance (TPR) and pulse pressure (PP$_{p}$) after adjustment for age, sex, race, heart rate, country, and BMI. Gray bars represent normal PP$_{p}$ and black bars are high PP$_{p}$. No interaction was found.
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 grounds. This apparent inconsistency is caused by different age-related peripheral amplification of central systolic pressure, because in young people magnitude of PP depends on levels of systolic BP, whereas in older populations diastolic BP is a stronger determinant. Franklin et al demonstrated that the prognostic effect of brachial PP on coronary heart disease was stronger than that of systolic BP. At each level of systolic BP, the risk was in fact higher when diastolic BP was lower, suggesting more severe arterial stiffness. This concept is generally accepted, although not unequivocally proven, in human studies. There is evidence of association of brachial PP with structural abnormalities of conduit arteries and there is evidence that both PP and other measures more directly associated with arterial stiffness share a similar pattern of relations with cardiovascular risk factors and prediction of mortality.

In this study, hypertensive individuals were divided on the basis of both the resistance element and the pulsatile element of the arterial tree, with the hypothesis that elevation of the pulsatile element defines more severe injury of the arterial tree. Our assumption has been that high brachial PP is not a cardiovascular risk factor (ie, cause of disease), such as arterial hypertension, but rather a marker of preclinical cardiovascular disease (ie, consequence of exposure), that is mathematically related to systolic and/or diastolic BP, but substantially depends on progressive impairment of arterial function. One limitation of this assumption is in the matching of the directly measured pulsatile element with the resistance element, which is computed from indirect parameters of flow and steady pressure.

Given the aforementioned limitation, our model predicts that in the presence of either normal or high peripheral resistance, brachial PP is associated with greater increase in LV mass and PP/SV (by estimated PP_{central}), supporting conclusions derived from the Framingham Heart Study, in which low diastolic BP and high PP are associated with increased coronary heart disease events at each level of systolic BP. This is consistent with our regression modeling using principal components in which the component representative of PP_{brachial} and age exhibit strong association with LV mass and PP/SV, 2 validated predictors of cardiovascular outcome, independent of the component representative of diastolic BP.

In this analysis, PP/SV is used as a surrogate estimate of arterial stiffness and has in fact the same units as a stiffness measure (mm Hg/mL per beat). However, it should be noted that PP/SV does not reflect elastic properties of conduit arteries and it changes with BP. Thus, it would be of interest to confirm relations of PP_{brachial} to more direct measures of central arterial stiffness using measures that are independent of BP. Because the measure of stiffness modeled on the 2-element Windkessel (such as PP/SV) can be affected by reflected waves from periphery, when reflection site is close to the heart, direct measurements of true arterial stiffness should validate the suggested conclusion of our analysis.

There is a potential tautology in relating PP_{brachial} with PP_{central}/SV. To minimize the mathematical tautology of this relation, we derived an estimate of PP_{central}, by a previously reported regression model, generated in a composite group of untreated hypertensive subjects and normotensive individuals, including age, to calculate the PP/SV ratio. The ratio PP_{central}/stroke volume was much less correlated with PP_{brachial} (r^2=0.14) than was the ratio of PP_{brachial} to stroke volume (r^2=0.57, P<0.0001 between slopes). The biological meaning of the association of PP_{brachial} with PP_{central}/SV goes in the same direction as the association of PP_{brachial} with LV mass, which is not affected by these mathematical considerations.

Finally, our estimate of central PP has not been validated in groups different from the ones analyzed in our original work. As a consequence, PP/SV ratio based on estimated central PP has not been validated directly. However, central BP by application tonometry has been invasively validated, which suggests that taking into account this limitation, our estimate might be an acceptable approximation for use on epidemiological scale.

Perspectives

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 other BP components, further research is required.
of systolic/diastolic BP for risk stratification) ultimately needs to be proven, using more direct measures of arterial stiffness and prospective studies.

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References
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