A Potent Predictor of Total Cardiovascular Risk in Hypertension

Paolo Verdecchia, Giuseppe Schillaci, Claudia Borgioni, Antonella Ciucci, Sergio Pede, Carlo Porcellati

Abstract—A wide pulse pressure (PP) is a marker of increased artery stiffness and high cardiovascular (CV) risk. To investigate the prognostic value of ambulatory PP, which is currently unknown, we studied 2010 initially untreated subjects with uncomplicated essential hypertension (mean age, 51.7 years; 52% men). All subjects underwent baseline procedures including 24-hour noninvasive ambulatory blood pressure (BP) monitoring. The mean duration of follow-up was 3.8 years (range, 0 to 11 years), and CV morbidity and mortality were the outcome measures. There were 200 major CV events (2.61 per 100 person-years), 36 of which were fatal (0.47 per 100 person-years). In the 3 tertiles of the distribution of office PP, the rate of total CV events (per 100 persons per year) was 1.38, 2.12, and 4.34, respectively, and that of fatal events was 0.12, 0.30, and 1.07 (log-rank test, both P<0.01). In the 3 tertiles of the distribution of average 24-hour PP, the rate of total CV events was 1.19, 1.81, and 4.92, and that of fatal events was 0.11, 0.17, and 1.23 (log-rank test, both P<0.01). After controlling for several independent risk markers including white coat hypertension and nondipper status, we found that ambulatory PP was associated with the biggest reduction in the –2 log likelihood statistics for CV morbidity (P=0.05 versus office PP). In each of the 3 tertiles of office PP, CV morbidity and mortality increased from the first to the third tertile of average 24-hour ambulatory PP (log-rank test, all P<0.01). Age, left ventricular hypertrophy, and nondipper status were independent predictors of CV mortality, and the further predictive effect of ambulatory PP (P=0.001) was marginally but not significantly superior to that of office PP and average 24-hour systolic BP. We conclude that ambulatory PP is a potent risk marker in essential hypertension. CV morbidity is more closely predicted by ambulatory than by office PP even after control for multiple risk factors. (Hypertension. 1998;32:983-988.)

Key Words: hypertension, arterial pulse pressure, hypertrophy, prognosis, blood pressure monitoring

An important basic mechanism of the rise in pulse pressure (PP) with age is believed to be the progressive stiffening of large arteries.1,2 A high PP may reflect already diseased arterial walls, with several adverse cardiac implications of potential prognostic value.3,4 In cross-sectional studies, PP showed a direct association with carotid atherosclerosis,3,4 left ventricular (LV) mass,5 and white matter lesions detected by MRI.6 From a prognostic viewpoint, an association was also independent of newer risk markers including LV mass at echocardiography and white coat hypertension.7,8,9,10,11

In a previous observational study from our laboratory, this association was independent of newer risk markers including LV mass at echocardiography and white coat hypertension.12

PP is affected by the alerting reaction evoked by the clinical visit.13 Thus, office PP could not be representative of the usual PP. In this setting, some studies suggest that ambulatory PP correlates with organ damage more closely than office PP does.14,15

The prognostic value of ambulatory PP is currently unknown. In this study, we analyzed the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) database12,16,17 to test the association between office PP, ambulatory PP, and CV morbidity and mortality in subjects with essential hypertension.

Methods

The PIUMA Study

The PIUMA study is a prospective registry of morbidity and mortality in white adult subjects with essential hypertension. The study design and procedures have been reported previously.12,16,17 All patients had office BP $140 mm Hg systolic and/or $90 mm Hg diastolic on at least 3 visits and fulfilled the following inclusion criteria: no previous antihypertensive treatment or treatment discontinued for at least 4 weeks before study; no clinical or laboratory evidence of heart failure, coronary artery disease, significant valvular

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From the Unità Operativa di Malattie Cardiovascolari, Ospedale Regionale Raffaello Silvestrini, Perugia (P.V., C.B., A.C., C.P.); the Divisione Medicina, Ospedale Beato G. Villa, Città della Pieve (G.S.); and the Servizio di Cardiologia, Ospedale N. Melli, San Pietro Vernotico (S.P.), Italy.


Reprint requests to Dr Paolo Verdecchia, Ospedale Generale Regionale “R. Silvestrini,” Unità Operativa di Malattie Cardiovascolari, Località Ponte della Pietra, 06156 Perugia PG, Italy. E-mail verdec@tin.it

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defects, secondary causes of hypertension, or other concomitant important disease; and at least 1 valid BP measurement per hour over the 24 hours. All subjects gave informed consent to the study, which was conducted in accordance with the declarations of Helsinki and Tokyo.

Procedures
The present analysis involved 2010 consecutive patients enrolled from June 1986 through December 1996. BP was measured by a physician with a mercury sphygmomanometer in the outpatient office in a quiet environment, with the subject sitting and relaxed for at least 10 minutes. The average of 3 measurements was used for analysis.

Ambulatory BP
Ambulatory BP was recorded using an oscillometric device (SpaceLabs 5200, 90202, and 90207) set to take a reading every 15 minutes throughout the 24 hours. Reading, editing, and analysis of data were done as previously described.12,16,17 White coat hypertension was defined as an average daytime ambulatory BP <130 mm Hg systolic and <80 mm Hg diastolic,12 and a nondipping pattern was defined as a night/day systolic BP ratio >0.899 in men or >0.909 in women.13 Daytime and nighttime BP were calculated using the “narrow fixed-clock intervals” (daytime period from 10 AM to 8 PM, nighttime period from midnight to 6 AM).20

Electrocardiography
Standard 12-lead ECG was recorded in all subjects at 25 mm/s and 1 mV/cm calibration. Tracings were coded and interpreted by 2 investigators without knowledge of other patient data. Interobserver differences occurred in <5% of readings and were resolved by consensus. Subjects with complete bundle-branch block, previous myocardial infarction, Wolff-Parkinson-White syndrome, or atrial fibrillation were excluded from the ECG analysis for LV hypertrophy. None of the subjects was treated with digitals. LV hypertrophy was tested using a score recently developed16 and prognostically validated17 in our laboratory (Perugia score), which requires positivity of ≥1 of the following 3 criteria: $S_{V3}+R_{V5} >2.4$ mV (men) or >2.0 mV (women), LV strain, or a Romhilt-Estes score of 5 or more points. Good-quality echocardiographic tracings of the LV were obtained in 1651 of these subjects (82%), but these data were not considered in the present analysis to maximize the number of patients available for assessment of outcome.

Follow-Up
All subjects were followed up by their family doctors, in cooperation with the outpatient office of the referring hospital, and treated with the aim of reducing office BP to <140/90 mm Hg using standard lifestyle and pharmacological measures. Diuretics, β-blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, and α₁-blockers, alone or in various combinations, were the antihypertensive drugs most frequently used. There were periodical contacts with family doctors and telephone interviews with patients to ascertain the vital status and the occurrence of major CV complications. All interviews were conducted without knowledge of patient data. Many of the patients continued to be periodically referred to our institutions for optimization of BP control. A major effort was recently undertaken to assess the vital status of all subjects.

End Point Evaluation
Hospital record forms and other source documents for patients who died or suffered a CV event were reviewed in conference by the authors of this study, without knowledge of results of ambulatory BP monitoring and other diagnostic procedures. CV events included new-onset coronary artery disease (myocardial infarction or angina with concomitant ischemic ECG changes), stroke, transient cerebral ischemia, symptomatic aortoiliac occlusive disease verified at angiography, thrombotic occlusion of a retinal artery documented at angiography, congestive heart failure requiring hospitalization, and renal failure requiring dialysis. The international standard criteria used to diagnose outcome events in the PIUMA study have been described elsewhere.13,17,21

Data Analysis
BMDP Statistical Software, version 7, was used to perform the analysis. Parametric data are reported as mean±SD. Standard descriptive and comparative statistical analyses were undertaken. For the subjects who experienced multiple events, survival analysis was based on the first event. Survival curves were estimated using the Kaplan-Meier product-limit method25 and were compared by the Mantel (log-rank) test.26 The effect of prognostic factors on survival was evaluated by the stepwise Cox semiparametric regression model.26 We tested the following variables: age (<40 years, 41 to 60 years, ≥60 years), sex (women, men), diabetes (no, yes), serum cholesterol (mmol/L), smoking habits (current smokers, previous smokers, never smokers), body mass index (kg/m²), LV hypertrophy at ECG using the Perugia score16,17 (no, yes), antihypertensive therapy at the follow-up contact (lifestyle measures, drug treatment), white coat hypertension (yes, no), and dipping pattern (nondippers, dippers). Age was analyzed as a categorical variable because of an abrupt increase of risk after age 60 years, with consequent failure to pass the linearity test. Systolic BP, diabetic BP, and PP were tested as either office or average 24-hour values, and the −2 log likelihood (L) statistic25 was used to compare the different models. This procedure compares different models fitted to the same set of survival data; the smaller the −2 log L value, the better the agreement between the model and the observed data.25 A significant difference between the −2 log L statistics provided by different methods indicates a better prediction of risk estimate provided by the method leading to the lowest −2 log L value. In 2-tailed tests, a value of $P<0.05$ was considered statistically significant.

Results
The main characteristics of the population studied are reported in Table 1. Seventy-nine percent of subjects (n=1596)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>2010</td>
</tr>
<tr>
<td>Known duration of hypertension, y</td>
<td>4.53±6</td>
</tr>
<tr>
<td>Duration of follow-up, y</td>
<td>3.81±2.4 (range, 1–10)</td>
</tr>
<tr>
<td>Age, y</td>
<td>52±12</td>
</tr>
<tr>
<td>Women, %</td>
<td>48</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>75±14</td>
</tr>
<tr>
<td>Height, cm</td>
<td>167±9</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.8±4</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.83±0.20</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>7.6</td>
</tr>
<tr>
<td>LV hypertrophy at ECG, %</td>
<td>16.2</td>
</tr>
<tr>
<td>Office values</td>
<td></td>
</tr>
<tr>
<td>Systolic, mm Hg</td>
<td>157±18</td>
</tr>
<tr>
<td>Diastolic, mm Hg</td>
<td>97±10</td>
</tr>
<tr>
<td>Pulse, mm Hg</td>
<td>60±17</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>79±10</td>
</tr>
<tr>
<td>Average 24-hour values</td>
<td></td>
</tr>
<tr>
<td>Systolic, mm Hg</td>
<td>138±15</td>
</tr>
<tr>
<td>Diastolic, mm Hg</td>
<td>87±10</td>
</tr>
<tr>
<td>Pulse, mm Hg</td>
<td>51±11</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>87±10</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD.
were classified as being in Joint National Committee VI stage I (41%) or stage II (38%), whereas the remaining subjects (n=414) were in stage III (21%). Prevalence of LV hypertrophy at ECG was 16.2%. Prevalence of white coat hypertension was 6% (n=117) and that of nondippers was 34% (n=685).

**Antihypertensive Therapy**
At the follow-up contact, 45% of the subjects were receiving lifestyle measures alone, 10% β-blockers alone or combined with other agents, 22% angiotensin-converting enzyme inhibitors or calcium antagonists alone or combined, and 23% other drug combinations. In tertiles of the distribution of baseline office PP, these frequencies of therapy were 55%, 10%, 20%, and 15% (first tertile); 45%, 11%, 21%, and 23% (second tertile); and 35%, 10%, 24%, and 31% (third tertile). In tertiles of the distribution of baseline ambulatory PP, these frequencies were 56%, 11%, 18%, and 15% (first tertile); 47%, 8%, 23%, and 22% (second tertile); and 33%, 11%, 24%, and 32% (third tertile). None of these differences among the 3 tertiles of office or ambulatory PP was statistically significant.

**CV Events**
During follow-up there were 200 total (fatal+nonfatal) CV morbid events (2.61 events per 100 person-years) at the cardiac (n=98), cerebral (n=79), or peripheral vascular (n=23) level. Thirty-six CV events were fatal (0.47 events per 100 patient-years). Specifically, there were 61 subjects with stroke (13 fatal), 32 with myocardial infarction (4 fatal), 15 with sudden cardiac death, 4 with cardiac death from other causes, 18 with transient cerebral ischemia, 25 with new-onset coronary artery disease, 7 with aortocoronary bypass surgery, 15 with heart failure requiring hospitalization, 17 with new-onset aortoiliac occlusive disease, 2 with occlusion of the retinal artery verified at fluoroangiography, and 4 with renal failure requiring dialysis. Total CV event rate (per 100 patient-years) was 0.94 in the subset with white coat hypertension versus 2.72 in that with ambulatory hypertension (P<0.001), and 1.64 in dippers versus 4.49 in nondippers (P<0.001).

**Role of PP: Univariate Analysis**
At entry, office and average 24-hour PPs were higher (all P<0.001) in the subjects who subsequently developed a CV event (71 and 59 mm Hg, respectively) than in those who did not (59 and 50 mm Hg, respectively). As shown in Figure 1, the rate of total CV events (per 100 patient-years) was 1.38, 2.12, and 4.34 in the first, second, and third tertile of office PP (log-rank test, P<0.001) and 1.19, 1.81, and 4.92 in the first, second, and third tertile of ambulatory PP (log-rank test, P<0.001), respectively. The rate of fatal CV events (Figure 2) was 0.12, 0.30, and 1.07 in the first, second, and third tertile of office PP (log-rank test, P<0.001) and 0.11, 0.17, and 1.23 in the first, second, and third tertile of ambulatory PP (log-rank test, P<0.001), respectively. Figures 3 and 4 show that for every tertile of office PP, the rate of total CV events (Figure 3) and fatal (Figure 4) CV events increased from the first to the third tertile of ambulatory PP (log-rank test, all P<0.05). In contrast, for every tertile of ambulatory PP, total and fatal event rate did not change with office PP.

**Role of PP: Multivariate Analysis**
Results are reported in Table 2 for CV morbidity and Table 3 for CV mortality. The relative risks and 95% confidence intervals associated with a 10-mm Hg increment in the corresponding BP component are reported.

**CV Morbidity**
After controlling for the other independent covariates (age, gender, LV hypertrophy, cholesterol, diabetes, smoking,
white coat hypertension, and nondipper status), we found that the addition of ambulatory PP to the model yielded a further significant reduction ($P < 0.006$) in the $-2 \log L$ statistics ($P < 0.05$ versus models with either office systolic BP, office PP, or 24-hour systolic BP).

**CV Mortality**

After controlling for the other independent covariates (age, LV hypertrophy, and nondipper status), we found that the addition of ambulatory PP to the model yielded a further significant reduction ($P = 0.001$) in the $-2 \log L$ statistics, which were marginally but not significantly different from those achieved by addition of office PP or average 24-hour systolic BP.

**Discussion**

This study demonstrates that ambulatory PP is a strong independent predictor of CV risk in apparently healthy subjects with essential hypertension. CV morbidity was better predicted by ambulatory PP than by office PP even after controlling for multiple risk factors.

**White Coat Effect and PP**

It has been shown that the rise in intra-arterial systolic and diastolic BP during the physician’s visit is 4 to 75 mm Hg (mean, 27 mm Hg) and 1 to 36 mm Hg (mean, 15 mm Hg), respectively. The bigger rise in systolic than diastolic BP implies an average increase in PP of about 12 mm Hg from before to during the visit. Consequently, office PP measurement may overestimate the usual levels of PP. It is generally believed that stroke volume, rapidity of ventricular ejection, viscoelastic properties of large arteries, and timing of reflected waves are important determinants of PP, although peripheral vascular resistance may also contribute. A transient sympathetic activation associated with the alerting reaction evoked by the visit may increase both size and velocity of LV emptying, with consequent rise in PP.

**Target Organ Damage and PP**

There is growing evidence from experimental and clinical studies that ambulatory PP is superior to office PP in predicting CV mortality and morbidity. For every tertile of office PP, CV mortality increased (log-rank test, all $P < 0.05$) from the first to the third tertile of ambulatory PP.

**TABLE 2. Results of Multivariate Analysis for Cardiovascular Morbidity**

<table>
<thead>
<tr>
<th>Variable Added to Model</th>
<th>Comparison</th>
<th>RR (95% CI)</th>
<th>$-2 \log L$ Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>&gt;60 vs ≤40</td>
<td>5.42 (2.45–12.0)</td>
<td>2222.4</td>
</tr>
<tr>
<td>LV hypertrophy</td>
<td>Yes vs no</td>
<td>1.85 (1.34–2.55)</td>
<td>2199.7</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes vs no</td>
<td>2.24 (1.55–3.25)</td>
<td>2180.7</td>
</tr>
<tr>
<td>Age, y</td>
<td>41–60 vs ≤40</td>
<td>2.56 (1.18–5.56)</td>
<td>2172.9</td>
</tr>
<tr>
<td>Smoking, cigarettes/d</td>
<td>&gt;20 vs 0</td>
<td>1.68 (1.07–2.64)</td>
<td>2165.2</td>
</tr>
<tr>
<td>WC hypertension</td>
<td>WC vs AH</td>
<td>0.30 (0.09–0.95)</td>
<td>2157.8</td>
</tr>
<tr>
<td>Dipping pattern</td>
<td>ND vs D</td>
<td>1.46 (1.06–2.01)</td>
<td>2152.1</td>
</tr>
<tr>
<td>Gender</td>
<td>Men vs women</td>
<td>1.44 (1.05–1.98)</td>
<td>2147.8</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>&gt;6.46 vs ≤5.17</td>
<td>1.43 (1.01–2.03)</td>
<td>2144.0</td>
</tr>
<tr>
<td>Expanded model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office systolic BP</td>
<td>10 mm Hg</td>
<td>1.12 (1.04–1.21)</td>
<td>2136.2</td>
</tr>
<tr>
<td>Office PP</td>
<td>10 mm Hg</td>
<td>1.20 (1.10–1.32)</td>
<td>2128.3</td>
</tr>
<tr>
<td>24-Hour systolic BP</td>
<td>10 mm Hg</td>
<td>1.23 (1.12–1.35)</td>
<td>2131.9</td>
</tr>
<tr>
<td>24-Hour PP</td>
<td>10 mm Hg</td>
<td>1.33 (1.17–1.51)</td>
<td>2125.0*</td>
</tr>
</tbody>
</table>

The expanded model includes all variables that entered the basic model plus either office systolic BP or office PP or average 24-hour systolic BP or average 24-hour PP. Office diastolic BP and average 24-hour diastolic BP did not yield statistical significance to enter the model.

RR indicates relative risk; CI, confidence interval; WC, white coat hypertension; AH, ambulatory hypertension; ND, nondippers; and D, dippers.

* $P < 0.05$ vs expanded model including either office systolic BP or office PP or average 24-hour systolic BP. Serum cholesterol levels of 6.46 and 5.17 mmol/L correspond to 250 and 200 mg/dL, respectively.
predicting target organ damage in hypertension. In animal studies, Christiansen and coworkers showed that intra-arterial PP recorded over 24 hours is an important determinant of artery media-lumen ratio. In hypertensive humans, average 24-hour intra-arterial PP showed a consistent association with LV mass, carotid intima-media thickness, and carotid cross-sectional area; such association was independent of age, obesity, and systolic and diastolic BP. In another study in subjects older than 60 years, a significant relation was found between media-lumen ratio of resistance vessels obtained from skin biopsies and average 24-hour PP, and this relation was independent of age and systolic and mean BP.

Prognostic Value of PP
Office PP is a major predictor of CV risk in the general population, in patients with hypertension, and in survivors of acute myocardial infarction. The rise in PP with age may reflect a gradual increase in the stiffness of the large arteries, which is mostly an effect of progression of atherosclerotic lesions. Indirect but solid evidence of the prognostic value of PP comes from the huge database of the Multiple Risk Factor Intervention Trial, in which systolic BP was a major predictor of all-cause, stroke, and coronary mortality at any level of diastolic BP. However, the assessment of the independent prognostic value of PP may be complicated by the confounding influence of comorbid risk markers, which may show an association with PP. For example, evidence is accumulating that LV hypertrophy at echocardiography and ambulatory BP are independent predictors of total CV risk. In a previous prospective analysis of the PIUMA database, office PP maintained an independent association with CV morbidity after adjustment for several covariates including LV hypertrophy at echocardiography, classified as present versus absent, and ambulatory BP, classified as white coat hypertension versus dippers versus nondippers.

In the present study, the prognostic value of the pulsatile component of ambulatory BP (ie, ambulatory PP) remained significant after controlling for a marker of low risk (ie, white coat hypertension) and a marker of increased risk (ie, a nondipping pattern), both derived from the steady component of ambulatory BP. It was also noteworthy that for every tertile of office PP, CV morbidity and mortality significantly increased from the first to the third tertile of ambulatory PP (Figures 3 and 4). However, multivariate analysis of CV mortality was unable to detect a statistically superior prognostic value of ambulatory PP over office PP or average 24-hour systolic PP, despite a trend in that direction (P value between 0.05 and 0.10).

Overall, these data indicate that the alerting reaction to office BP measurement weakens the relation between PP and total CV risk and that ambulatory PP offers a more precise estimate of risk.

Limitations
The present study has some limitations. First, because at least 20 outcome events are needed for each independent variable retained in the final model of a multivariate analysis, our study has a good statistical power to detect significant independent associations between different covariates and a pool of events reflecting CV morbidity and mortality, but not to analyze the cardiac and cerebrovascular events separately. Second, because no more than 40% of our subjects repeated 24-hour ambulatory BP monitoring during follow-up, we cannot establish the prognostic value of the serial changes in PP during treatment. Third, because our data have been obtained in a 100% white population, results may not be extended to other racial groups. Fourth, the possible collinearity between some measures of office and ambulatory BP included in the multivariate model might complicate the analysis by excluding variables not necessarily unrelated to outcome; however, the use of the –2 log L statistics in this study allowed a direct and unbiased comparison between competing models.

Conclusion
Ambulatory PP was a potent independent predictor of total CV risk in initially untreated white subjects with essential
hypertension. These data indicate that ambulatory PP is a more accurate marker than office PP of increased arterial stiffness or already diseased arteries. This and other demonstrations of the prognostic value of PP provide a strong and stimulating rationale to investigate in prospective outcome trials whether PP is superior to systolic and diastolic BP as a target for antihypertensive strategy.

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