Different Prognostic Impact of 24-Hour Mean Blood Pressure and Pulse Pressure on Stroke and Coronary Artery Disease in Essential Hypertension

Paolo Verdecchia, MD; Giuseppe Schillaci, MD; Gianpaolo Reboldi, MD, MSc, PhD; Stanley S. Franklin, MD; Carlo Porcellati, MD

Background—We tested the hypothesis that the steady and pulsatile components of blood pressure (BP) exert a different influence on coronary artery disease and stroke in subjects with hypertension.

Methods and Results—We analyzed data on 2311 subjects with essential hypertension. All subjects (mean age 51 years, 47% women) underwent off-therapy 24-hour ambulatory BP monitoring. Over a follow-up period of up to 14 years (mean 4.7 years), there were 132 major cardiac events (1.20 per 100 person-years) and 105 cerebrovascular events (0.90 per 100 person-years). After adjustment for age, sex, diabetes, serum cholesterol, and cigarette smoking (all \( P < 0.01 \)), for each 10 mm Hg increase in 24-hour pulse pressure (PP), there was an independent 35% increase in the risk of cardiac events (95% CI 17% to 55%). Twenty-four–hour mean BP was not a significant predictor of cardiac events after controlling for PP. After adjustment for age, sex, and diabetes (all \( P < 0.05 \)), for every 10 mm Hg increase in 24-hour mean BP, the risk of cerebrovascular events increased by 42% (95% CI 19% to 69%), and 24-hour PP did not yield significance after controlling for 24-hour mean BP. Twenty-four–hour PP was also an independent predictor of fatal cardiac events, and 24-hour mean BP was an independent predictor of fatal cerebrovascular events.

Conclusions—In subjects with predominantly systolic and diastolic hypertension, ambulatory mean BP and PP exert a different predictive effect on the cardiac and cerebrovascular complications. Although PP is the dominant predictor of cardiac events, mean BP is the major independent predictor of cerebrovascular events. (Circulation. 2001;103:2579–2584.)

Key Words: hypertension • hypertrophy • prognosis • blood pressure • epidemiology

Pulse pressure (PP) is a well-established marker of cardiovascular risk in different clinical settings.\(^1^–^8\) However, not all studies examined the prognostic effect of PP on cardiac and cerebrovascular events separately. In a general population study, PP predicted cardiovascular but not cerebrovascular mortality.\(^2\) In a recent analysis of the Medical Research Council Mild Hypertension Trial, sphygmomanometric PP was a strong independent predictor of coronary events, whereas stroke was best predicted by mean blood pressure (BP).\(^9\) A study with intra-arterial BP monitoring also provided indirect evidence of a greater predictive effect of PP on cardiac events than on cerebrovascular events.\(^9\)

Because clinical visits are frequently associated with alerting reactions,\(^1^0\) office PP might not reflect the usual levels of PP in the single individual. Indeed, a composite pool of cardiovascular events was better predicted by ambulatory PP than by office PP in a recent study.\(^1^1\) The object of the present study, using off-therapy 24-hour ambulatory BP monitoring, was to examine separately the prognostic effect of PP on cardiac and cerebrovascular events. We used the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) database, a prospective, ongoing, Italian observational study of subjects with essential hypertension.

Methods

The PIUMA Study

The design and procedures of the PIUMA study have been reported previously.\(^4^,^1^0\) All patients had office systolic BP \( \geq 140 \) mm Hg and/or diastolic BP \( \geq 90 \) mm Hg on at least 3 visits. Main inclusion criteria were as follows: the absence of previous antihypertensive treatment or treatment withdrawn for at least 4 weeks; no current or previous diagnosis of heart failure, coronary artery disease, significant valvular defects, secondary causes of hypertension, or other concomitant important disease; and \( \geq 1 \) valid BP measurement per hour over the 24 hours. Diabetes was diagnosed by a fasting glucose \( \geq 7.77 \) mmol/L (140 mg/dL) or current treatment with oral hypoglycemic drugs or insulin. A physician measured BP 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 considered for analysis. Ambulatory BP was recorded with an oscillometric device (SpaceLabs 5200, 90202, and 90207), which was set to take a reading every 15 minutes throughout the 24 hours. The spontaneous day-to-day variability of ambulatory BP was assessed in some of these patients. Standard 12-lead ECG was recorded in all subjects at 25 mm/s and 1-mV/cm calibration. None of the subjects was treated with digitalis. Left ventricular (LV) hypertrophy was tested by use of a score recently developed in our laboratory (Perugia score), which requires positivity of ≥1 of the following 3 criteria: SV, +RaVL, ≥2.4 mV (men) or >2.0 mV (women), LV strain, or a Romhilt-Estes score of ≥5 points.

Follow-Up
Follow-up was mostly in the charge of family doctors, in cooperation with the outpatient office of the referring hospital. Treatment was aimed at reducing office BP to <140/90 mm Hg by using standard lifestyle and pharmacological measures. Diuretics, β-blockers, ACE inhibitors, calcium channel blockers, and α-blockers, alone or in various combinations, were the antihypertensive drugs most frequently used. Periodic contacts with family doctors and telephone interviews with patients were arranged to ascertain the vital status and the occurrence of major cardiovascular events. All interviews were conducted without knowledge of the patient’s data.

End-Point Evaluation
Hospital record forms and other source documents of patients who died or suffered a cardiovascular event were reviewed in conference by the authors of the present study. The international standard criteria used to diagnose outcome events in the PIUMA study have been described elsewhere. Cardiac events included myocardial infarction, unstable angina with concomitant ischemic ECG changes, coronary artery surgery or angioplasty, sudden cardiac death, and congestive heart failure. Cerebrovascular events included stroke and transient cerebral ischemia.

Data Analysis
Statistical analysis was performed using SPSS (SPSS Inc) and SAS-Stat (SAS Institute). Parametric data are reported as mean±SD. For the subjects who experienced multiple events, survival analysis was based on the first event. Survival curves were estimated by using the Kaplan-Meier product-limit method and compared by the Mantel (log-rank) test. The effect of prognostic factors on survival was evaluated by stepwise Cox model. Cardiac and cerebrovascular events were analyzed separately. For both, we first tested a baseline model including age, sex (men or women), family history of premature cardiovascular disease (yes or no), diabetes (yes or no), serum cholesterol (mmol/L), serum triglycerides (mmol/L), smoking habits (nonsmokers, current smokers, former smokers, body mass index (kg/m²), and antihypertensive treatment at follow-up (lifestyle measures alone, diuretics and β-blockers alone or combined, ACE inhibitors and calcium antagonists alone or combined, or other drug combinations). Subsequent improvements in the model fitting were tested by entering, one at a time, the various BP components (systolic BP, diastolic BP, mean BP, and PP) by using both the office and the average 24-hour ambulatory values. Mean BP was calculated as diastolic BP+(PP/3). In 2-tailed tests, a value P<0.05 was considered statistically significant.

Results
The main characteristics of the study population at entry into the PIUMA registry are shown in Table 1. Combined systolic and diastolic hypertension was present in 1704 subjects (73.7%), isolated systolic hypertension was present in 328 (14.2%), and isolated diastolic hypertension was present in 279 (12.1%). At the last follow-up contact, 41.8% of the subjects were receiving lifestyle measures alone, 10.6% were receiving β-blockers alone or combined with other agents, 20.3% were receiving ACE inhibitors or calcium antagonists alone or combined, and 27.3% were receiving other drug combinations.

Over a mean follow-up period of 4.7 years (range 0 to 14 years), there were 132 cardiac events (1.20 per 100 person-years), 13.6% of which were fatal, and 105 cerebrovascular events (0.90 per 100 person-years), 17.1% of which were fatal. There were 47 subjects with myocardial infarction, 31 with new-onset angina and ST segment changes, 12 with coronary bypass surgery or angioplasty, 17 with sudden cardiac death, 25 with heart failure requiring hospitalization, 78 with stroke, and 27 with transient ischemic attack. The main baseline characteristics of the subjects with and without cardiac or cerebrovascular events are shown in Table 1. Figure 1 shows the 4-year age-adjusted and risk factor–adjusted probability (from the Cox analysis) of cardiac and cerebrovascular events by increasing levels of 24-hour mean BP and PP. As shown in Figure 2, cardiac events increased more strikingly with increasing 24-hour PP, whereas cerebrovascular events increased more with mean 24-hour mean BP. Division points for quartiles were 96, 103, and 110 mm Hg for the average 24-hour mean BP and 44, 49, and 56 mm Hg for the average 24-hour PP.

Multivariate Analysis
After adjustment for a baseline model including age (P<0.001), sex (P<0.01), diabetes (P<0.01), serum cholesterol (P<0.01), and cigarette smoking (P<0.01), the risk of cardiac events increased by 35% (95% CI 17% to 55%) for each 10 mm Hg increase in 24-hour PP. When both 24-hour PP and 24-hour mean BP were forced into the same model, the latter did not yield statistical significance (P=0.09). None of the measures of office BP yielded significance when added, one at a time, to the baseline model. After adjustment for age (P<0.01), sex (P<0.05), and diabetes (P<0.01), the risk of cerebrovascular events increased by 42% (95% CI 19% to 69%) for every 10 mm Hg increase in 24-hour mean BP. In this model, 24-hour BP did not yield significance (P=0.35) after controlling for mean BP. As shown in Table 2, the average 24-hour PP was also an independent predictor of fatal cardiac events, and 24-hour mean BP was an independent predictor of fatal cerebrovascular events. None of the other tested covariates (see data analysis) achieved significance.

Discussion
The principal new finding of the present study was that in a large sample of subjects with predominantly systolic and diastolic hypertension whose age spanned 8 decades, the risk of cardiac complications of elevated BP showed a strong, positive, and independent association with its pulsatile component (PP) but not with its steady component (mean BP), whereas the risk of cerebrovascular complications showed a similarly strong, positive, and independent association with its steady component but not with its pulsatile component. These associations persisted after adjustment for the significant influence of numerous risk factors. The use of ambula-
BP improved the accuracy of prognostic prediction, as noted in previous outcome studies.15

Pathophysiology
An increased stiffness of large elastic arteries is a well-recognized mechanism of the increase in PP with age.16,17 Increased PP predicts coronary artery stenosis,18 carotid artery lesions,19-21 and LV hypertrophy.21,22 A possible basis for the strong impact of elevated PP on the risk of cardiac events1-7 might be the unfavorable balance between early reflection of the pressure wave in the aorta during systole (further increasing LV wall stress and oxygen requirement)23 and the potentially impaired coronary flow at low levels of diastolic BP. However, brachial PP may not be a reliable marker of central PP because of the progressive peripheral amplification of the pressure wave, which tends to decrease with age and to increase with height.24,25

Several mechanisms may explain the dominant prognostic impact of the steady component of BP (ie, mean BP) on the subsequent cerebrovascular events. The small penetrating end arteries, which supply the medial and basal portions of the brain and brain stem, seem to be particularly vulnerable to the adverse effects of high BP, inasmuch as these arteries arise directly from the main arterial trunks.26 If we assume that diastolic BP is also a steady BP component over which cyclic pulsatile stress does occur, it is worth noting that the association of diastolic BP with stroke is steeper than that with myocardial infarction27 and that the reduction in systolic and diastolic BP induced by antihypertensive treatment lowers the risk of stroke to a greater extent than the risk of myocardial infarction.28 However, the role of mean BP as a surrogate of peripheral vascular resistance tends to become less reliable with aging. Because mean BP is twice as sensitive to diastolic than to systolic BP (mean BP = 1/3 systolic BP + 2/3 diastolic BP), the leveling off and the eventual fall in diastolic BP with aging, as opposed to the continued rise in systolic BP, lead to a progressive underestimation of peripheral vascular resistance by the mean BP equation.29

Previous Studies Involving Combined Systolic/Diastolic Hypertension
Studies in the general population2 and in subjects with hypertension6,11 have suggested an association of sphygmonometric PP with cardiac events and an association of mean BP with cerebrovascular events. In the European

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### TABLE 1. Main Baseline Characteristics of Subjects With and Without Future Cardiac and Cerebrovascular Events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Population</th>
<th>Cardiac Events</th>
<th>Cerebrovascular Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No Event</td>
<td>Event</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n=2179)</td>
<td>(n=132)</td>
</tr>
<tr>
<td>Age, y</td>
<td>51±12</td>
<td>51±12</td>
<td>59±12*</td>
</tr>
<tr>
<td>Sex, % men</td>
<td>52.9</td>
<td>52.4</td>
<td>61.4†</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>7.3</td>
<td>6.1</td>
<td>27.3*</td>
</tr>
<tr>
<td>Cigarette smoking, %</td>
<td>23</td>
<td>22.1</td>
<td>32.6</td>
</tr>
<tr>
<td>Office systolic BP, mm Hg</td>
<td>157±19</td>
<td>157±19</td>
<td>163±20*</td>
</tr>
<tr>
<td>Office diastolic BP, mm Hg</td>
<td>97±10</td>
<td>97±10</td>
<td>96±12</td>
</tr>
<tr>
<td>Office mean BP, mm Hg</td>
<td>117±11</td>
<td>117±11</td>
<td>118±12</td>
</tr>
<tr>
<td>Office PP, mm Hg</td>
<td>60±17</td>
<td>60±17</td>
<td>67±20*</td>
</tr>
<tr>
<td>Office HR, bpm</td>
<td>75±10</td>
<td>75±10</td>
<td>73±11†</td>
</tr>
<tr>
<td>24-h systolic BP, mm Hg</td>
<td>137±15</td>
<td>137±15</td>
<td>146±18*</td>
</tr>
<tr>
<td>24-h diastolic BP, mm Hg</td>
<td>87±10</td>
<td>87±10</td>
<td>88±11†</td>
</tr>
<tr>
<td>24-h mean BP, mm Hg</td>
<td>104±11</td>
<td>103±11</td>
<td>107±12*</td>
</tr>
<tr>
<td>24-h PP, mm Hg</td>
<td>51±11</td>
<td>50±10</td>
<td>58±14*</td>
</tr>
<tr>
<td>24-h HR, bpm</td>
<td>75±9</td>
<td>75±9</td>
<td>73±10</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.63±1.4</td>
<td>5.57±1.3</td>
<td>6.57±2.1*</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>87.2±22</td>
<td>86.6±21</td>
<td>95.2±31†</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.57±1.1</td>
<td>5.56±1.1</td>
<td>5.80±1.2†</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.26±0.31</td>
<td>1.27±0.30</td>
<td>1.14±0.28†</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.60±1.0</td>
<td>3.58±0.96</td>
<td>3.90±0.97†</td>
</tr>
<tr>
<td>Total/HDL cholesterol ratio</td>
<td>4.66±1.34</td>
<td>4.61±1.31</td>
<td>5.40±1.59*</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.68±1.13</td>
<td>1.67±1.14</td>
<td>1.78±0.96</td>
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<tr>
<td>Uric acid, mmol/L</td>
<td>0.283±0.08</td>
<td>0.281±0.08</td>
<td>0.312±0.08*</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>4.20±0.39</td>
<td>4.20±0.38</td>
<td>4.29±0.45*</td>
</tr>
<tr>
<td>LV hypertrophy, %</td>
<td>17.8</td>
<td>16.8</td>
<td>35.7*</td>
</tr>
</tbody>
</table>

Values are mean±SD. HR indicates heart rate. *P<0.01; †P<0.05.
Working Party on Hypertension in the Elderly (EWPHE) study, which included patients with elevated values of both systolic and diastolic BP, mean BP predicted stroke (hazards ratio [HR] 1.91, 95% CI 1.05 to 2.18) but not coronary events (HR 1.09, 95% CI 0.77 to 1.35) after adjustment for PP, whereas PP did not predict stroke (HR 1.10, 95% CI 0.90 to 1.36) after adjustment for mean BP.

Previous Studies Involving Isolated Systolic Hypertension
In a meta-analysis of the prognostic value of PP in the EWPHE, Systolic Hypertension in Elderly in Europe (Syst-Eur), and Systolic Hypertension in Elderly Chinese (Syst-China) studies, PP predicted both coronary events and stroke after controlling for mean BP, whereas the predictive effect of mean BP on both types of events was not significant after controlling for PP. However, a dominant predictive value of PP over mean BP on both coronary events and stroke was present only in the Syst-Eur and Syst-China studies, which included patients with isolated systolic hypertension, but not in the EWPHE study, which included patients with both systolic and diastolic hypertension. In a meta-analysis of 8 studies in elderly subjects with isolated systolic hypertension, the risk of death was directly associated with systolic BP and inversely associated with diastolic BP, thus emphasizing the prognostic value of PP.

In the broad population of the Systolic Hypertension in the Elderly Program (SHEP), mean BP and PP were both independent determinants of stroke risk; however, stroke risk increased more with mean BP (by 20% for every 10 mm Hg) than with PP (by 11% for every 10 mm Hg).

The results of the present study support the hypothesis that elevated peripheral vascular resistance, estimated by mean BP, directly contributes to stroke risk. Because the mean age of our population was 51 years, the majority (73.7%) had systolic and diastolic hypertension, whereas a minority (14.2%) had isolated systolic hypertension. Thus, our large and relatively unselected middle-aged population was suitable for assessing the independent contribution of both mean BP and PP. In contrast, previous studies that examined elderly individuals (mean age >70 years) with isolated systolic hypertension systematically underestimated peripheral vascular resistance by the mean BP equation.

Collinearity Between Variables
Mean BP and PP are associated variables. In the present study, mean BP showed an association with PP (r=0.41) and diastolic BP (r=0.85), and these coefficients held for the

Figure 1. Four-year age-adjusted and risk factor-adjusted probability of cardiac (top panels) and cerebrovascular (bottom panels) events by increasing levels of 24-hour mean BP (left panels) and PP (right panels). Filled squares denote fatal events; filled circles denote total events.

Figure 2. Cardiac (left) and cerebrovascular (right) events in relation to ambulatory mean BP and PP.
average 24-hour ambulatory values ($r=0.28$ and $0.95$, respectively). In contrast, diastolic BP did not show any consistent association with PP, either considering the office ($r=-0.01$) or ambulatory ($r=-0.06$) values. The collinearity between PP and mean BP suggests that both BP components contribute to the risk of cardiac and cerebrovascular events in our hypertensive population (Figure 2) but that the independent impact of PP was stronger for the prediction of cardiac events and that the independent impact of mean BP was stronger for the prediction of cerebrovascular events.

**Therapeutic Implications**

Our findings raise the hypothesis that the risk of coronary artery disease in hypertensive subjects could be reduced to a greater extent than the risk of stroke by narrowing the pulsatile component of BP (ie, by reducing PP) at any level of reduction in the steady BP component (ie, mean BP). Retrospective analyses of existing outcome studies and, especially, prospective trials are needed to clarify this issue. ACE inhibitors and vasopeptidase inhibitors seem to improve distensibility of large arteries by preventing the progressive arterial stiffening resulting from collagen deposition. Low-dose diuretics are also effective in reducing arterial stiffness.

**Conclusions**

Our prospective observational cohort study indicates that elevated peripheral vascular resistance appears to be more damaging to the brain and that increased large artery stiffness appears to be more damaging to the heart in unselected middle-aged individuals with predominantly systolic and diastolic hypertension.

**References**


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