Relation of Pulse Pressure and Blood Pressure Reduction to the Incidence of Myocardial Infarction

Shantha Madhavan, Wee Lock Ooi, Hillel Cohen, Michael H. Alderman

Abstract The prognostic value of pretreatment pulse pressure as a predictor of myocardial infarction and the relation of pulse pressure and in-treatment diastolic blood pressure reduction to myocardial infarction were investigated in a union-sponsored systematic hypertension control program. In a prospective study, 2207 hypertensive patients with a pretreatment systolic blood pressure greater than or equal to 160 mm Hg and/or diastolic pressure greater than or equal to 95 mm Hg were stratified by the degree of diastolic fall: large (L), ≥18; moderate (M), 7 to 17; small (S), ≤6 mm Hg. During an average follow-up of 5 years, 132 cardiovascular events (50 myocardial infarctions, 23 strokes) were observed. Myocardial infarction rates per 1000 person-years were positively related to pulse pressure (PP1, ≥46; PP2, 47 to 62; PP3, ≥63 mm Hg) were further stratified according to tertile of pulse pressure (PP1, ≤46; PP2, 47 to 62; PP3, ≥63 mm Hg). Wide pulse pressure was identified as a predictor of myocardial infarction (PP3 versus [PP1+PP2]: relative risk [RR]=2.2, 95% confidence interval [CI]=1.2-4.1), controlling for other known risk factors by Cox regression. A curvilinear relation (resembling a J shape) between diastolic fall and myocardial infarction was observed in patients with the widest pulse pressure, PP3 (L, 9.5; M, 3.9; S, 11.2; L versus M: RR=2.5, 95% CI=1.0-6.2; S versus M: RR=2.9, 95% CI=1.1-8.0). Even after adjusting for age, sex, race, and previous cardiovascular disease using the Mantel-Haenszel method, this relation persisted in PP3 (L versus M: RR=2.6, 95% CI=1.0-6.5; S versus M: RR=3.3, 95% CI=1.2-9.5). A wide pretreatment pulse pressure (≥63 mm Hg) was associated with subsequent cardiovascular complications and identified that subgroup of hypertensive patients at greatest risk of myocardial infarction from either too large or too small a fall in diastolic blood pressure.

Key Words • blood pressure • pulse • myocardial infarction

Therapeutic decision making and management in patients with mild to moderate hypertension are complicated by the wide variation in their clinical characteristics. Clinicians therefore have sought more precise means to describe the outlook for individual patients. One approach has been to use different measures of baseline blood pressure (BP), such as 24-hour recordings, response to stress, and variability of BP, to prognostically stratify patients. As Sleigh and others have suggested, a wide pulse pressure (PP) may reflect atherosclerotic disease and stiff arteries and identify individuals with an increased risk. We have assessed the value of PP as a means of identifying patients with preexisting cardiovascular disease (CVD) who are at increased risk of myocardial infarction (MI).

Moreover, because it has been previously demonstrated in this population that a curvilinear (J-shaped) relation exists between the extent of BP reduction (as achieved through hypotensive therapy) and the occurrence of MI, we have further explored this relation after stratifying patients according to their pretreatment PP.

We now report that a wide PP measured before treatment is associated with an increased incidence of in-treatment MI. In addition, it was only among patients with a wide PP that the curvilinear relation of diastolic BP fall to MI was found. Thus, pretreatment PP not only provides valuable prognostic information in itself but also is a useful tool in the identification of those patients in whom too large a treatment-induced fall in diastolic BP is likely to be associated with an increased risk of MI.

Methods

Recruitment of Patients

Study patients were drawn from employee participants in an occupationally based, union-sponsored, systematic hypertension control program. Of 2287 patients who entered treatment between May 1973 and June 1990 and who had an untreated systolic BP greater than or equal to 160 mm Hg and/or diastolic BP greater than or equal to 95 mm Hg, 80 with follow-up of less than 2 months were excluded, yielding a study population of 2207 patients of whom 93% had a follow-up of at least 6 months or more with an average of 4.8 years. The study was carried out according to a protocol approved by the institutional review board.

Patient Evaluation

At initial patient evaluation, information was obtained on demographic characteristics, behavioral and medical histories, physical examination, electrocardiographic findings, routine clinical chemistry measures, and BP measurements. The initial evaluation was repeated and interval history recorded at annual physical examinations.
Treatment Plan

Treatment was based on a modified, stepped-care protocol that started with hydrochlorothiazide and, since 1979, with propranolol as an alternate drug of first choice. After 1981, adrenergic blockers, calcium channel blockers, and angiotensin-converting enzyme (ACE) inhibitors were also prescribed as first-line drug choices. Drugs were added to achieve a diastolic BP less than 90 mm Hg and a systolic BP less than 160 mm Hg.

Blood Pressure Measurements

All BP readings at pretreatment and follow-up visits were taken by a trained nurse using a standard sphygmomanometer. At each visit, the average of the second and third readings in a set of three (taken with the patient in the sitting position) was recorded as the BP for the day. Pretreatment BP was recorded at a visit 2 weeks before treatment was started. The “final BP” used in this analysis was the average of all available BP values recorded during the 6 months preceding a CVD event or, in patients who did not have an event, all readings obtained in the last 6 months of follow-up, up to and including the last visit. BP fall was the difference between pretreatment and final BP. The three strata of diastolic BP fall used in the present study were large (L: ≥18 mm Hg), moderate (M: 7 to 17 mm Hg), and small (S: ≤6 mm Hg), derived from our earlier report. The moderate fall was based on a midpoint fall of 12 mm Hg with a range of 5 mm Hg in either direction from the midpoint. Because stratification by change in systolic BP fall produced no statistically significant association with CVD in the same study as well as in the present study, it was not used in the present analysis.

Pretreatment BP was the difference between systolic and diastolic BP at initial evaluation before therapy. Tertiles of PP were used as cut points for the study of three groups with an equivalent number of patients and increasing level of PP for the observation of the dose-response relation. Patients were stratified by tertile of PP into three categories (PP1, ≤46; PP2, 47 to 62; PP3, ≥63 mm Hg).

Morbidity and Mortality

Morbidity events were defined using the format of the International Classification of Diseases Manual, Ninth Revision, Clinical Modification (ICD-9-CM). Events of principal interest were MI (code 410) and cerebrovascular disease (codes 430 through 434 and 436 through 438, henceforth referred to as strokes). Deaths were categorized as either CVD or non-CVD events. For patients with multiple events during follow-up, only the first event was included in this analysis. Data were recorded on computer-compatible forms and processed for computer storage and analysis.

Morbidity and fatal events were first ascertained by a nurse who systematically monitored reports by patients, family members, or friends on hospitalizations or deaths. Further confirmation of events was obtained through careful review of hospital and medical charts and death certificates by the research staff.

Among the 2207 study patients, 263 events (197 morbid and 66 mortal) were observed: CVD, 132; cancer, 15; and other non-CVD, 116. Of the 132 CVD events, 50 (28 nonfatal, 22 fatal) were MIs, 23 (17, 6) strokes, 18 (16, 2) revascularization/unstable angina/congestive heart failure, and 41 (22, 19) other CVD. Confirmation by hospital records and/or death certificates was available for 41 of 50 (82%) MIs, 15 of 23 (65%) strokes, and 16 of 19 (84%) other CVD deaths. The remainder were validated by private physicians, family, friends, or union records.

Statistical Analysis

Descriptive statistics based on initial patient characteristics were computed to compare the study patients grouped by PP category. Means and standard deviations for initial and final BP measurements were obtained for each PP group, and differences were tested for statistical significance using the Student’s t test.

Cause-specific event rates (per 1000 person-years) were also computed for each PP group. Relative risk (RR) and 95% confidence interval (CI) were calculated to compare event rates between strata. Incidence rates of MI (per 1000 person-years) were estimated for the three diastolic BP fall categories (L, M, and S) within each PP stratum to examine the interrelation between PP, BP fall, and MI and the presence of the J-shaped curve. Further analysis included bivariate and multivariate stratified analyses to estimate the incidence of MI and the relative risks controlling for selected risk factors using the Mantel-Haenszel procedure. The Cox proportional-hazards model was applied to assess the independent association of pretreatment PP and MI occurrence during treatment, after other potential confounding or competing factors were accounted for. In addition, PP was replaced by pretreatment systolic BP in the Cox model to compare the two measures as predictors of MI events.

Results

Patient Characteristics

Based on the frequency distribution of the 2207 hypertensive patients, the PP tertile cut points were fixed as less than or equal to 46 mm Hg, 47 to 62 mm Hg, and greater than or equal to 63 mm Hg to classify patients into PP1, PP2, and PP3 strata (Table 1). Tertiles by PP segregated study patients with sharply different demographic, clinical, and laboratory findings. Although smoking behavior was similar, significant differences were observed in age, gender, race, previous CVD (history of CVD events including MI, stroke, angina, and other heart trouble) as reported by the patient at the initial evaluation before treatment, left ventricular hypertrophy (LVH) on electrocardiogram, body mass index, and cholesterol levels in the three PP strata. Those with the widest PP compared with those with the narrowest were substantially older and included more females and whites. This group also had more evidence of preexisting CVD as expressed by a prior history of CVD and LVH by electrocardiogram. Finally, although PP3 patients tended to be lighter (mean body mass index: 27.1 [PP3] versus 28.5 [PP1] kg/m², P<.001), they had higher mean serum cholesterol levels (6.06 mmol/L [233 mg/dL] versus 5.80 [222], P<.001).

Pulse Pressure and Other Blood Pressure Measures

The means and standard deviations of systolic and diastolic BP, PP, and mean arterial pressure (MAP) at initial and final evaluations by PP tertiles are presented in Table 2. Although initial MAP and systolic BP were both higher for patients in PP3 than PP1, diastolic BP was significantly lower. In other words, a greater PP and MAP were the result of a higher systolic BP (accounting for 92% of the difference in PP between PP1 and PP3) and a lower diastolic BP. After treatment, MAP of all three PP groups fell significantly, but because the fall in PP3 was greatest, the gap in final MAP between groups narrowed substantially, although PP2 and PP3 were still statistically but probably not clinically different from PP1. However, the characteristics of the BP change that accompanied the reduction in MAP fell differed in the
TABLE 1. Baseline Characteristics of Previously Untreated Patients by Pulse Pressure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PP1, % (n=735)</th>
<th>PP2, % (n=726)</th>
<th>PP3, % (n=746)</th>
<th>P (PP3 vs PP1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥55 years</td>
<td>15.6</td>
<td>31.5</td>
<td>61.3</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Male</td>
<td>81.6</td>
<td>72.9</td>
<td>66.0</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>White</td>
<td>35.9</td>
<td>39.9</td>
<td>51.7</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Smoker</td>
<td>28.2</td>
<td>28.4</td>
<td>32.6</td>
<td>.074</td>
</tr>
<tr>
<td>Previous CVD</td>
<td>8.4</td>
<td>11.2</td>
<td>13.1</td>
<td>.005</td>
</tr>
<tr>
<td>LVH</td>
<td>6.9</td>
<td>12.1</td>
<td>16.5</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>BMI ≥29 kg/m²</td>
<td>40.1</td>
<td>39.8</td>
<td>28.6</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Cholesterol ≥6.37 mmol/L (245 mg/dL)</td>
<td>27.5</td>
<td>31.0</td>
<td>34.8</td>
<td>&lt; .003</td>
</tr>
</tbody>
</table>

PP1 indicates pulse pressure ≤46 mm Hg; PP2, 47 to 62 mm Hg; PP3, ≥63 mm Hg; CVD, cardiovascular disease; LVH, left ventricular hypertrophy by electrocardiography; and BMI, body mass index.

highest and lowest PP groups. A fall in diastolic BP was almost entirely responsible for the improvement in patients with a narrow PP (PP1). For those with the widest PP (PP3), both a systolic and diastolic fall contributed to the drop in MAP. In addition, final diastolic BP was significantly lower (by 5 mm Hg) in patients in PP3 compared with PP1, maintaining the difference observed initially.

The overall average diastolic BP decline was 13.0 mm Hg. Patients in PP2 and PP3 had similar reductions in diastolic BP, which were significantly (P<.01) greater than in PP1 (PP1, 11.8; PP2, 13.8; PP3, 13.3 mm Hg).

In the entire group, previously defined cut points for diastolic fall (L, ≥18; M, 7 to 17; S, <6 mm Hg) produced three subgroups similar in proportion to those observed in our earlier study (27.4%, 49.9%, and 22.7%, respectively). Furthermore, the distribution of patients experiencing a large, medium, and small fall was similar for the two lower strata (PP1: 24%, 50%, 26%; PP2: 27%, 56%, 17%), but PP3 (32%, 43%, 25%) included significantly more patients who experienced a large fall. The mean final diastolic BP values for patients experiencing a large, medium, and small fall, respectively, in the PP3 stratum (82±9, 86±8, and 90±9 mm Hg) were lower than their corresponding levels in the PP1 (85±7, 90±5, and 97±5) and PP2 (84±7, 90±5, and 98±6) strata.

**Drug Use**

At entry, 66% of patients were prescribed (alone or in combination with other drugs) a diuretic, 20% a β-blocker, and 7% an ACE inhibitor. The proportions of patients initially on these three drugs were similar in the three PP strata—diuretics: 63%, 66%, and 70% in PP1, PP2, and PP3, respectively; β-blockers: 23%, 19%, and 19%; and ACE inhibitors: 8%, 8%, and 4%. Compared with initial therapy, at final visit diuretics were less commonly used in all three PP strata (39%, 47%, and 57%) but increased from the lowest to the highest PP stratum; prescriptions for β-blockers increased overall but were similar by strata (30%, 25%, and 25%), and those for ACE inhibitors increased nearly threefold (22%, 21%, and 16%). However, there was no rapid or greater reduction in diastolic BP among patients

TABLE 2. Blood Pressure Profiles of Previously Untreated Patients by Pulse Pressure

<table>
<thead>
<tr>
<th>Blood Pressure, mm Hg</th>
<th>PP1 (n=735)</th>
<th>PP2 (n=726)</th>
<th>PP3 (n=746)</th>
<th>P (PP3 vs PP1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>139.8±9.0</td>
<td>157.6±8.8</td>
<td>178.4±14.8</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>102.5±6.3</td>
<td>103.6±7.3</td>
<td>99.0±11.6</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>37.3±6.5</td>
<td>54.1±4.5</td>
<td>79.3±12.7</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>MAP</td>
<td>114.9±6.6</td>
<td>121.6±7.5</td>
<td>125.5±11.2</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Final*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>133.8±11.2</td>
<td>139.8±12.8</td>
<td>149.1±15.5</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>90.7±6.9</td>
<td>89.7±7.5</td>
<td>85.7±9.2</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>43.1±8.1</td>
<td>50.1±11.0</td>
<td>63.4±15.1</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>MAP</td>
<td>105.1±7.4</td>
<td>106.4±8.1</td>
<td>106.8±9.3</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

PP1 indicates pulse pressure ≤46 mm Hg; PP2, 47 to 62 mm Hg; PP3, ≥63 mm Hg; and MAP, mean arterial pressure. Values are mean±SD.

* Average of blood pressure readings up through 6 months before an event or before and including the last visit for patients without cardiovascular disease.
patients on ACE inhibitors (−12.26 mm Hg) compared with those on diuretics (−12.26 mm Hg) or β-blockers (−13.17 mm Hg).

Morbidity and Mortality

The average length of follow-up for patients was similar (4.7, 4.8, and 5.0 person-years in PP1, PP2, and PP3, respectively). A preponderance of MIs (28 of 50) and nearly half of all strokes (11 of 23) occurred in PP3 (Table 3). There was a significant difference in the incidence of MI and total CVD between PP1 and PP3. CVD deaths accounted for 74% (49 of 66) of all-cause mortality. Of these CVD deaths, 57% (28 of 49) occurred in PP3 at a rate of 7.5 per 1000 person-years, which was four times higher (P=.0004) than the rate (1.7) in PP1.

In a multivariate Cox regression analysis (Table 4) of the entire sample with PP as a categorical variable (PP3 [highest] versus PP1+PP2), PP3 was observed to be an independent risk factor for MI (RR=2.2, 95% CI=1.2-4.1) even after adjusting for age, sex, race, smoking, prior CVD, LVH, and cholesterol level. A similar observation was made for CVD. However, when PP was entered in the model as a continuous variable, it was not independently associated with MI or CVD.

In another Cox model, in which PP was replaced by initial systolic BP keeping all other factors constant, systolic BP was not independently related to MI as either a continuous (P=.15) or categorical (P=.06) variable.

Curvilinear Relation

The interrelation between PP, diastolic BP fall, and incidence of MI is illustrated in Table 5 and the Figure. The curvilinear relation between MI incidence and diastolic fall for the entire group followed a J-shaped curve or more closely a U-shaped curve, with greater risk at both lower and higher levels of fall (L, 5.9; M, 3.1; S, 6.9), having RR values of 1.9 and 2.3 and 95% CI values of 1.0-3.7 and 1.1-4.6, respectively, for L and S compared with M as referent. However, in the two lower PP strata, individually or pooled, the MI rates within diastolic BP fall categories were not significantly different but instead showed somewhat random patterns (PP1: 3.2, 2.8, 5.5 [L, M, S, respectively]; PP2: 3.4, 2.6, 2.3; pooled: 3.3, 2.7, 4.3).

In contrast, for patients in PP3, who were overall at the highest MI risk (7.5 per 1000 person-years), the presence of a significant curvilinear relation of MI to the degree of diastolic reduction was demonstrated by a V-shaped curve (Figure) connecting the observed incidence rates at three discrete points of diastolic fall (L, 9.5; M, 3.9; S, 11.2); L versus M: RR=2.5 (95% CI=1.0-6.2) and S versus M: RR=2.9 (95% CI=1.1-8.0). The

| Table 3. Cause-Specific Morbidity and Mortality (Per 1000 Person-Years) by Pulse Pressure |
|------------------------------------------|----------------|----------------|----------------|
| Event                             | PP1 (n=735) | PP2 (n=726) | PP3 (n=746) | RR (95% CI) (PP3 vs PP1) |
| Myocardial Infarction             | 3.5 (12)    | 2.9 (10)    | 7.5 (28)    | 2.2 (1.1-4.2)          |
| Stroke                            | 1.2 (4)     | 2.3 (8)     | 2.9 (11)    | 2.5 (0.8-7.7)          |
| CVD                               | 5.2 (18)    | 6.6 (23)    | 13.6 (51)   | 2.6 (1.6-4.4)          |
| CVD deaths                        | 1.7 (6)     | 4.3 (15)    | 7.5 (28)    | 4.3 (1.9-9.6)          |

PP1 indicates pulse pressure ≤46 mm Hg; PP2, 47 to 62 mm Hg; PP3, ≥63 mm Hg; RR, relative risk; CI, confidence interval; and CVD, cardiovascular disease (myocardial infarction, stroke, and deaths from other cardiovascular disease). Figures in parentheses are number of events.

| Table 4. Proportional-Hazards Regression Model (Best Fit) for Incidence of Myocardial Infarction In Treated Hypertensive Patients |
|------------------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Variable*                                | Coefficient   | SEM            | P              | Hazard Ratio (CI) |
| Pulse pressure (high=1)                  | 0.780         | 0.327          | .017           | 2.2 (1.2-4.1)   |
| Sex (male=1)                             | 1.414         | 0.480          | .003           | 4.1 (1.6-10.5)  |
| Age at entry (per 10 years)†             | 0.031         | 0.016          | .056           | 1.4 (1.0-1.9)   |
| Smoker (yes=1)                           | 0.545         | 0.298          | .068           | 1.7 (0.9-3.1)   |
| History of CVD (yes=1)                   | 0.770         | 0.356          | .031           | 2.2 (1.1-4.4)   |
| Cholesterol (per 1.17 mmol/L) (45 mg/dL)† | 0.004         | 0.002          | .080           | 1.2 (1.0-1.4)   |

CI Indicates 95% confidence interval; CVD, cardiovascular disease.
*Not found to be predictive were race, left ventricular hypertrophy, and body mass index at baseline.
†For continuous variables, the hazard ratio was for the increase in the variables by the interval (approximately 1 SD) shown in parentheses.
Table 5. Incidence of Myocardial Infarction (Per 1000 Person-Years) by Pulse Pressure and Degree of Diastolic Blood Pressure Reduction

<table>
<thead>
<tr>
<th>Pulse Pressure</th>
<th>Diastolic BP Fall</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L (n=604)</td>
<td>M (n=1102)</td>
</tr>
<tr>
<td>PP1 (&lt;46 mm Hg)</td>
<td>3.2 (3)</td>
<td>2.8</td>
</tr>
<tr>
<td>PP2 (47 to 62 mm Hg)</td>
<td>3.4 (4)</td>
<td>2.6</td>
</tr>
<tr>
<td>PP3 (≥83 mm Hg)</td>
<td>9.5 (14)</td>
<td>3.9</td>
</tr>
<tr>
<td>Total</td>
<td>5.9 (21)</td>
<td>3.1</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; L, large fall of ≥18 mm Hg; M, medium fall of 7 to 17 mm Hg; S, small fall of ≤6 mm Hg; RR, relative risk; CI, confidence interval; and PP1, PP2, PP3, pulse pressure tertiles.

*RR (95% CI) adjusted for sex, race, age, and previous cardiovascular disease was 2.6 (1.0-6.5) for L vs M and 3.3 (1.2-9.5) for S vs M by multivariate stratified analysis.

Nonlinear relation was confirmed by applying a test for a linear trend in proportions of MI events in the three diastolic BP fall groups of PP3. The χ² for deviations from linearity was 5.4, significant at P=.02 with 1 degree of freedom.

Similar analysis replacing diastolic BP by tertile of systolic BP fall (L, ≥27; M, 6 to 26; and S, ≤5 mm Hg) showed no significant differences between MI rates of the three fall categories (L, M, and S, respectively) for PP1 (0.0, 4.4, 3.0), PP2 (2.1, 3.1, 3.2), and PP3 (7.9, 6.9, 9.1).

To determine whether PP was more effective than age or systolic BP in identifying the subgroup of patients most likely to exhibit the curvilinear relation, we stratified all study patients by age (<55, ≥55 years). A J-shaped curve was demonstrated in both strata, although it was not significant. Likewise, stratifying by tertile of systolic BP, the MI incidence rates followed the J-shaped curve in the highest tertile. However, in contrast to the highest PP stratum, the difference in rates between a large and moderate diastolic fall (7.34 versus 4.16 per 1000 person-years) was not significant (P=.24).

Stratified Analysis

Exposure-specific MI rates were calculated in the PP3 stratum for each degree of diastolic BP fall (L, M, and S) after dichotomizing by selected risk factors to estimate RR for L and S with M as the referent group. In all categories, MI rates in the referent group M were the lowest, and the curvilinearity of RR reflected by L versus M and S versus M, respectively, was accentuated for men (2.4, 95% CI=0.9-6.4; 3.0, 95% CI=1.0-8.9), those 55 years or older (2.9, 95% CI=1.0-8.9; 3.3, 95% CI=1.0-10.8), and those with a previous history of CVD (5.9, 95% CI=0.9-38.1; 8.0, 95% CI=1.2-53.8). Even after controlling (separately) for each risk factor by applying the Mantel-Haenszel method, the curvilinear relation between MI and diastolic fall persisted, varying according to the type of characteristics. In general, for all risk factors the adjusted RR values for L (range, 2.3 to 2.5; P=.047 to .085) were lower than those for S (range, 2.9 to 3.0; P=.031 to .044).

Based on the observations from the bivariate analysis, multivariate stratified analysis was done to further test the J-shaped relation in PP3 selecting sex, race, age, and previous CVD as appropriate variables for stratification. Both L and S diastolic BP falls were significantly associated with an increased risk of MI (L versus M: RR=2.6, 95% CI=1.0-6.5; S versus M: RR=3.3, 95% CI=1.2-9.5) after controlling for the confounding effects of these four risk factors (Table 5).

Discussion

The principal findings of this study are that a large pretreatment PP is a simple clinical marker for subsequent cardiovascular complications and that a wide PP identifies that subgroup of hypertensive patients in whom the curvilinear relation of BP fall to MI can best be demonstrated. In contrast to PP, no other measure of pretreatment BP identified patients at greatest risk of...
CVD or that subgroup most likely to display the J-shaped curve. The direct and positive relations between systolic and diastolic BP levels and CVD are well established.\textsuperscript{13-18} Because of the variable relation between systolic and diastolic pressures, there has been an effort to determine a more precise estimate of BP involving these two measures. MAP and PP, the steady and pulsatile components of BP, respectively, are two descriptions proposed to be of additional clinical value. A wide PP is known to be associated with higher levels of CVD risk factors, including a tendency toward increased cardiac mass by echocardiography.\textsuperscript{19,20} Moreover, in one previous large prospective study of hypertensive individuals, a wide PP was an independent risk factor of CVD death.\textsuperscript{21}

Physiologically, PP describes the oscillation around the MAP (calculated as diastolic BP plus one third PP) and is influenced by hemodynamic mechanisms that differ from MAP, which reflects steady flow in the aorta and its major arteries during a given cardiac cycle.\textsuperscript{22} The mechanisms influencing PP are the velocity of ventricular ejection, the viscoelastic properties of the arterial wall, and the timing of the reflected waves.

Increased PP may be explained by increased ventricular ejection in younger patients with systolic hypertension, but more commonly, with increasing age it is likely to be due to a decrease in compliance of the arterial system as the elasticity of the aorta and other large arteries declines\textsuperscript{22}—in other words, as atherosclerosis and the risk of coronary artery disease are increased.

In rats, PP is a major risk factor for increased vascular resistance, and its reduction by treatment is important in normalizing small-artery structure.\textsuperscript{23} A wide PP may also be responsible for altering vascular structure in chronic hypertension.\textsuperscript{24}

In this analysis, although initial diastolic BP is a component of both PP and diastolic BP fall, we believe it is legitimate to consider the contribution of these two indexes to the course of hypertensive patients independently. Pretreatment PP, the difference between systolic and diastolic BP values measured at entry, is a point estimate. By contrast, diastolic BP fall, the difference between initial and final readings, is a time-dependent measure that reflects the effect of treatment. The lack of correlation between these two measures reaffirms their independence.

Although clinical trials of antihypertensive treatment\textsuperscript{25-28} have demonstrated the overall benefit of BP reduction, the effect of therapeutic intervention has approximated what epidemiologic studies might have predicted only in the case of stroke, whereas the effect on MI has been less than expected.\textsuperscript{29} Recent studies\textsuperscript{30-33} have suggested that the final attained diastolic BP may influence outcome. More recently, we demonstrated that the extent of diastolic BP fall rather than the actual attained level (although the two are generally similar) better predicts MI incidence.\textsuperscript{7}

Cruickshank et al\textsuperscript{21} have suggested that the J-shaped relation of BP reduction to MI may be limited to only those individuals with preexisting coronary artery disease. Recently, the Framingham experience\textsuperscript{34} revealed that the J-shaped curve relation for diastolic BP and coronary heart disease deaths was limited to patients who already had an MI. Because patients with a wide PP are most likely to have coronary heart disease, we applied this strategy to identify high-risk hypertensive patients as a surrogate for less-convenient measures to identify coronary heart disease as a clinically practical test of the hypothesis of Cruickshank et al.

Patients with a wide PP included a higher percentage of older patients, whites, and those with more previous CVD, LVH, and elevated cholesterol levels. Even though they were less likely to be male or obese, their MI rates were highest and they alone exhibited the curvilinear relation to BP fall. In fact, both large and small diastolic BP falls were the measures of BP independently associated with an increased incidence of MI in this group. Moreover, the nonlinear relation between BP fall and MI persisted even after controlling for age, sex, race, and previous history of CVD. These findings are in contrast to those reported from the Systolic Hypertension in the Elderly Program (SHEP) study,\textsuperscript{35} in which no J-shaped relation was observed. However, these two populations varied in their characteristics. The present study patients had primarily diastolic hypertension in contrast to those with isolated systolic hypertension in the SHEP study. The patients in the PP3 stratum were much younger (mean age, 57 years) than the SHEP participants, although 61% were 55 years or older. Also, they were drawn from a working population, so it can be assumed that they had a higher overall level of health than the SHEP study patients, who were much older with a mean age of 77 years. Also, the SHEP patients were not stratified by PP, and therefore a direct comparison of the two studies is not possible.

Because large reductions in diastolic BP did occur among patients in each pretreatment PP stratum, perhaps a large reduction in diastolic BP (in contrast to the small overall diastolic fall in SHEP) during the course of lowering systolic BP may uniquely compromise coronary perfusion and therefore adversely affect the heart.\textsuperscript{36} Patients with a wide PP were more likely to experience a large BP fall and if they did also have an increased risk of MI. Both phenomena can be attributed to the effects of treatment or the consequences of underlying cardiac status.

Ultimately, to resolve the issue of whether the J-shaped curve is merely an associated phenomenon or actually a cause of MI, a prospective study testing the effect of various levels of final diastolic BP or diastolic BP fall is required. Patients with a wide PP may be an appropriate population in which to resolve this issue. Pending that resolution, however, large BP reductions should be approached with caution in patients with wide PP values. However, these data do not provide a mandate to recommend alterations in the treatment of hypertension.

In summary, the present analysis demonstrated that a large pretreatment PP (≥63 mm Hg) is independently associated with subsequent CVD and particularly MI. But a wide PP not only distinguishes those hypertensive patients most likely to experience MI but may also provide a convenient tool for identification of those patients most likely to experience either a large (>18 mm Hg) or small (<6 mm Hg) diastolic BP fall in treatment, and more importantly, to have a heightened risk of MI associated with that BP reduction.
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