Mean Arterial Pressure: A Better Marker of Stroke in Patients with Uncontrolled Hypertension in Rural Areas of China

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Abstract

Objective The purpose of this study was to compare the association of pulse pressure (PP) and mean arterial pressure (MAP) with stroke in uncontrolled hypertensive subjects.

Methods A total of 9,901 uncontrolled hypertensive subjects were included in a cross-sectional study in 62 villages of Fuxin county of Liaoning Province, China.

Results Among the 9,901, 406 cases of ischemic stroke and 145 cases of cerebral hemorrhage were identified. Older age, male gender, increased SBP, higher DBP, and history of hyperlipemia were positively associated with both ischemic stroke and cerebral hemorrhage by multivariate logistic regression analysis. However, the odds ratios (ORs) of drinking for ischemic stroke and cerebral hemorrhage were 0.407 (95%CI: 0.304-0.544) and 0.595 (95%CI: 0.377-0.940), respectively. An increase of 10 mmHg of MAP had ORs of 1.430 (95%CI: 1.332-1.535) for ischemic stroke and 1.359 (95%CI: 1.220-1.514) for cerebral hemorrhage. The OR of PP (per 10 mmHg increase) for ischemic stroke was 1.085 (95%CI: 1.026-1.148). Subjects with the fourth quartile of PP and MAP had ORs of 1.555 (95%CI: 1.127-2.146) ischemic stroke and 5.127 (95%CI: 3.452-7.616) for cerebral hemorrhage, with the first quartile as the reference group. The OR of the fourth quartile of MAP for cerebral hemorrhage was 5.935 (95%CI: 2.932-12.012). There was no significant association between PP and cerebral hemorrhage. In sensitivity analysis, ORs of standard MAP for ischemic stroke were higher than those of PP in each stratified age subgroup.

Conclusions Increased MAP and PP were significant markers of ischemic stroke and cerebral hemorrhage was only associated with increased MAP. MAP was more closely associated with stroke than PP in patients with uncontrolled hypertension.

Key words: pulse pressure, mean arterial pressure, stroke, hypertension, epidemiology

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Introduction

Pulse pressure (PP), defined as the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP), is a pulsatile component of the blood pressure (BP) curve as opposed to mean arterial pressure (MAP), which is a steady component (1). In the past decade, PP and MAP are well-established markers of cardiovascular risk in different clinical settings (1-4). In a general population study, PP predicted cardiovascular but not cerebrovascular mortality (5). In a recent analysis of Medical Research Council Mild Hypertension Trial, sphygmomanometric PP was a predictor of coronary events and MAP was a better predictor of stroke than PP (6). A study of 24-hour BP monitoring also provided evidence that PP is the dominant predictor of cardiac events; MAP is the major independent predictor of cerebrovascular events (7). Whereas, results form some epidemiological studies indicate that PP is a better predictor of fatal stroke than MAP (8). In summary, there is controversy...
about the role of PP in stroke and whether MAP or PP is better associated with stroke remains unclear. In this study, we investigated the effect of PP on ischemic stroke and cerebral hemorrhage in uncontrolled hypertensive subjects aged with 35 to 75 years old and compared the effects of PP and MAP on stroke.

### Methods

#### Study population and data collection

This is a large-scale cross-sectional study. Subjects were collected with a multi-stage, stratified clustering sampling scheme in 62 villages of Fuxin county of Liaoning province, China from July 2004 to July 2006. A total of 9,901 uncontrolled hypertensive subjects aged 35 to 75 years were recruited in the study. Uncontrolled hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg regardless of receiving antihypertensive medication. Informed consent was obtained from all subjects and the local medical ethics committee approved the study. Stroke and risk factors were collected with an epidemiological survey. Stroke was defined as a history of cerebrovascular events (ischemic stroke and cerebral hemorrhage), documented by either cranial computed tomography (CT) or magnetic resonance scan (within the past 24 months before inclusion). A local doctor measured BP (three times in the left arm) using an electric sphygmomanometer after the subject had been at rest in the sitting position for ≥5 minutes. The mean value of the 3 separate SBP and 3 separate DBP measurements were used to determine the reported BP for that examination. Heart rate was also collected with an electric sphygmomanometer. PP was calculated as the difference between SBP and DBP. MAP was calculated as DBP plus one-third times (SBP minus DBP). Risk factors included age, sex, body mass index (BMI), smoking, drinking alcohol, history of hyperlipemia, and history of diabetes. Information on age, sex, smoking (≥10 cigarettes per day) and drinking everyday were based on self-report. The weight and height of subjects were measured while they were wearing light clothes and no shoes. BMI was calculated as weight (kg)/height (m²). Diabetes and hyperlipemia were defined as a history of physician-diagnosed report. Secondary hypertensions were excluded.

#### Statistical analysis

Continuous variables were given as mean ± SD and categorical variables as percentage in each subgroup. A one-way analysis of variance (ANOVA) and the chi-square test were used to compare continuous and categorical differences, respectively. Risk factors for ischemic stroke and cerebral hemorrhage were analyzed separately by multivariate logistic regression. Possible risk factors such as age, sex, BMI, SBP, DBP, heart rate, smoking, drinking, history of hyperlipemia and diabetes were analyzed, but PP and MAP were not used as independent parameters. Because PP and MAP were both derived from SBP and DBP and were correlated with SBP or DBP.

The relationships between PP, MAP and stroke were categorized into quartiles for each subgroup. Multivariate logistic regression models were used to calculate the odds ratio (OR) of stroke, with the first quartile as the reference group, respectively. A linear trend across quartiles of PP and MAP was tested with an ordinal variable. Possible risk factors for stroke such as age, sex, BMI, heart rate, smoking, drinking, history of hyperlipemia and diabetes were adjusted by multivariate logistic regression. We did not combine MAP and PP into 1 model because of their high intercorrelations. To compare these similar entities, we standardized variables (subtracted the mean and divided by the standard deviation) and fitted each in a separate multivariate model. Separate multivariate logistic models were considered for the following age groups: 35 to 44, 45 to 54, 55 to 64, 65 to 75 years. The resulting ORs were compared. All analyses were performed with SPSS statistical software version 12.0. A 2-tailed probability value of <0.05 was considered to be statistically significant.

#### Results

The present large-scale study of 9,901 patients consisted of 50.4% men and mean age was 54 years (range 35 to 75 years). We identified a total of 551 cases (ischemic stroke, 406 cases; cerebral hemorrhage, 145 cases) of prevalent stroke. The mean values of average SBP, DBP, PP and MAP were 155.83 ± 20.72 mmHg, 93.25 ± 11.82 mmHg, 62.58 ± 19.01 mmHg, 114.11±12.49 mmHg, respectively.

The baseline characteristics of characteristics of uncontrolled hypertensives with and without stroke (ischemic stroke and cerebral hemorrhage) are presented in Table 1. As expected, patients with ischemic stroke and cerebral hemorrhage were of older age, and had higher levels of average SBP, DBP, PP and MAP than subjects without stroke (all \(P<0.001\)). There was no significant difference in heart rate and BMI in the different groups (\(P>0.05\)). A higher ratio of male gender, history of hyperlipemia and diabetes was observed in patients with ischemic stroke and cerebral hemorrhage. Inversely, patients with ischemic stroke and cerebral hemorrhage had a lower ratio of drinking alcohol. No significant statistically ration of smoking was observed between patients with and without stroke (\(P>0.05\)).

Multivariate logistic regression analysis was used to evaluate the independent significance of associated factors. Table 2 shows the adjusted ORs and 95% confidence interval (CI) for ischemic stroke and cerebral hemorrhage. We found that older age, male gender, increased SBP, increased DBP, and a history of hyperlipemia or diabetes were positively associated with both ischemic stroke and cerebral hemorrhage. Higher BMI was only associated with cerebral hemorrhage. Drinking alcohol was negatively associated with both ischemic stroke and cerebral hemorrhage in patients with uncontrolled hypertension.
Table 1. Baseline Characteristics of Uncontrolled Hypertensives with and without Stroke (Ischemic Stroke and Cerebral Hemorrhage)

<table>
<thead>
<tr>
<th>Variables</th>
<th>No stroke (N=9350)</th>
<th>Ischemic stroke (N=406)</th>
<th>Cerebral hemorrhage (N=145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53.6±8.10±11.40</td>
<td>61.5±8.6±10.70</td>
<td>61.0±8.9±10.70</td>
</tr>
<tr>
<td>Average SBP, mmHg</td>
<td>155.02±20.41</td>
<td>169.65±20.90±13.26</td>
<td>169.37±21.72±12.76</td>
</tr>
<tr>
<td>Average DBP, mmHg</td>
<td>92.91±11.66</td>
<td>99.21±13.29±10.42</td>
<td>98.57±12.14±11.34</td>
</tr>
<tr>
<td>Average PP, mmHg</td>
<td>62.11±18.87</td>
<td>70.44±19.2±13.45</td>
<td>70.81±20.6±12.76±11.35</td>
</tr>
<tr>
<td>Average MAP, mmHg</td>
<td>113.6±12.26</td>
<td>122.6±13.46±10.71</td>
<td>122.17±12.76±11.01</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>76.36±10.31</td>
<td>76.54±9.71±7</td>
<td>76.93±11.01±7</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.73±3.27</td>
<td>23.41±3.99±7</td>
<td>24.17±4.42±7</td>
</tr>
<tr>
<td>Female, %</td>
<td>50.2</td>
<td>39.4±8</td>
<td>42.1</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>45.7</td>
<td>43.3±8</td>
<td>40.7</td>
</tr>
<tr>
<td>Drinking, %</td>
<td>33.9</td>
<td>20.7±8</td>
<td>23.4±8</td>
</tr>
<tr>
<td>History of hyperlipemia, %</td>
<td>6.3</td>
<td>33.5±8</td>
<td>26.9±8</td>
</tr>
<tr>
<td>History of diabetes, %</td>
<td>0.7</td>
<td>2.7±8</td>
<td>3.4±8</td>
</tr>
</tbody>
</table>

SBD: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MAP: mean arterial pressure; BMI: body mass index.

Table 2. Risk Factors for Ischemic Stroke and Cerebral Hemorrhage by Multivariate* Logistic Regression

<table>
<thead>
<tr>
<th>Variables</th>
<th>Ischemic stroke</th>
<th>Cerebral hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (1 year increased)</td>
<td>1.06±(1.03-1.09)</td>
<td>1.06±(1.04-1.10)</td>
</tr>
<tr>
<td>SBP (1 mmHg increased)</td>
<td>1.01±(1.01-1.02)</td>
<td>1.01±(1.01-1.03)</td>
</tr>
<tr>
<td>DBP (1 mmHg increased)</td>
<td>1.02±(1.01-1.03)</td>
<td>1.01±(1.01-1.03)</td>
</tr>
<tr>
<td>Heart rate (1 beats/min increased)</td>
<td>0.99±(0.98-1.00)</td>
<td>1.00±(0.98-1.01)</td>
</tr>
<tr>
<td>BMI, (1 kg/m² increased)</td>
<td>0.97±(0.94-1.01)</td>
<td>1.04±(1.02-1.08)</td>
</tr>
<tr>
<td>Female (versus male)</td>
<td>0.41±(0.32-0.52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (yes versus no)</td>
<td>0.95±(0.73-1.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Drinking (yes versus no)</td>
<td>0.40±(0.30-0.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of hyperlipemia</td>
<td>5.64±(4.44-7.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of diabetes (yes versus no)</td>
<td>1.76±(0.82-3.81)</td>
<td>0.120</td>
</tr>
</tbody>
</table>

SBD: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MAP: mean arterial pressure; BMI: body mass index.

The ORs of PP and MAP for risk of ischemic stroke and cerebral hemorrhage are shown in Table 3. An increase of 10 mmHg of MAP had ORs of 1.430 (95%CI: 1.332-1.535) for ischemic stroke and 1.359 (95%CI: 1.220-1.514) for cerebral hemorrhage. The OR of PP (per 10 mmHg increase) for ischemic stroke was 1.085 (95%CI: 1.026-1.148). Next we examined similar multivariate models but based on quartiles of average PP and MAP. Subjects with the fourth quartile of PP and MAP had ORs of 1.555 (95%CI: 1.127-2.146) ischemic stroke and 5.127 (95%CI: 3.452-7.616) for cerebral hemorrhage, with the first quartile as the reference group. The OR of the fourth quartile of MAP for cerebral hemorrhage was 5.935 (95%CI: 2.932-12.012). Furthermore, a linear trend across quartiles of PP and MAP was tested with an ordinal variable (Table 3). No significant association was observed between PP and cerebral hemorrhage.

In sensitivity analysis, we considered age stratified into 4 age subgroups (35 to 44, 45 to 54, 55 to 64, and 65 to 75 years) and compared the age-specific, multivariate ORs of ischemic stroke and cerebral hemorrhage for standard average PP and MAP (Figs. 1 and 2). There was a pattern of declining ORs with age of standard average MAP for ischemic stroke, whereas standard average PP. In every stratified age, ORs with age of standard average MAP for ischemic stroke were significantly larger than those of PP.

Discussion

The main findings of our study was that increased MAP and PP were significant markers of ischemic stroke and MAP was better associated with ischemic stroke than PP. Cerebral hemorrhage was only associated with increased MAP in patients with uncontrolled hypertension.

It is well known that BP is usually characterized by its pulsatile and steady components. The pulsatile component, estimated by PP, represents BP variation and is affected by left ventricular ejection fraction, large-artery stiffness, early pulse wave reduction, and heart rate (9, 10). The steady component, estimated by MAP, is a function of left ventricular contractility, heart rate, and vascular resistance and elasticity averaged over time (11). Our study including middle-aged and older subjects had been sufficiently powered to examine the association between PP, MAP and stroke in rural areas of China. Data from our study indicated

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that PP and MAP were markers of ischemic stroke in uncontrolled hypertensive subjects. In addition, MAP was more closely associated with ischemic stroke morbidity than PP in each age subgroup. It is possibly because MAP, a steady component reflects the resistance of the microvascular network, and PP, another component corresponds to large artery stiffness and wave reflections (1).

Physiologically, 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, in as much as these arteries arise directly from the main arterial trunks (12). However, the role of MAP 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, the leveling off and the eventual fall in diastolic BP with aging, as opposed to the continued rise in systolic BP, leads to a progressive underestimation of peripheral vascular resistance by the mean BP equation.

In the present study, PP was also a marker of ischemic stroke in uncontrolled hypertensive subjects, which were not similar to other results (5, 13-15). Physiologically speaking,
Figure 2. Age-specific ORs and 95% CIs of cerebral hemorrhage for standard Pulse Pressure and Mean Arterial Pressure when correcting for age, sex, body mass index, structural modifications of small arteries or rarefaction of microvessels are strongly associated with hypertension and traditionally considered to be responsible for high MAP. That is to say, a given level of MAP, and hence a given degree of microvascular network development, is required to optimize aortic Windkessel function (1). This approach may explain why, in a large population with a given genetic and environmental background (16), a Gaussian BP distribution is observed and therefore concords with the phenomenon of BP tracking, which is commonly observed in human populations. This pathophysiological mechanism fits with the predictive value of PP and arterial stiffness on CV morbidity and mortality. Rizzoni D et al (17) proved that structural alterations of small artery walls are a significant CV risk factor in hypertensive subjects but in association with increased PP.

Moreover, MAP was also independently associated with cerebral hemorrhage. But, PP was not associated with cerebral hemorrhage in our study. The possible reason was the lower prevalence of cerebral hemorrhage in our selected specified sample population in rural areas of China. Further study on association between PP and cerebral hemorrhage should be performed in the future in China.

Data from Framingham suggest that antihypertensive treatment may not confound the association between BP and coronary heart disease (18). So we selected uncontrolled hypertensive subjects in order to supply modest strategy to stroke detection in clinical therapy. In the present study, patients with ischemic stroke and cerebral hemorrhage were older and the adjusted ORs were 1.066 (95%CI: 1.053-1.078) for ischemic stroke and 1.061 (95%CI: 1.042-1.081) by logistic regression analysis. Male gender has been shown to be a risk factor for ischemic stroke and cerebral hemorrhage. Health education for stroke should be focused on male gender and older people in patients with uncontrolled hypertension. Consistent with the previous studies (19-21), increased SBP level, higher DBP level and history of hyperlipemia were risk factors for ischemic stroke and cerebral hemorrhage. Therefore reducing the level of BP and improving lipemia are very important to prevent stroke (22). In our study, drinking alcohol was negatively associated with ischemic stroke and cerebral hemorrhage, which was not found in other studies (23). The possible reason was that patients with stroke had begun cessation of drinking alcohol by suggestions of local doctor. Our study indicated that smoking had no association with ischemic stroke and cerebral hemorrhage, however smoking and BMI were significantly associated with hypertension, which was an important risk factor for stroke (24, 25). So, cessation of smoking and decreased BMI is also necessary for primary prevention of stroke.

Some limitations should also be considered in light of these results. First, having an observational nature, our study cannot prove a causal relationship of PP and MAP with stroke. It should be distinguished in some prospective studies. Second, the patients we observed were nonfatal stroke, not included fatal stroke, may be a selection bias. In conclusion, increased MAP and PP were significant markers of ischemic stroke and cerebral hemorrhage was only associated with increased MAP. Anyway, MAP was more closely associated with stroke than PP in patients with uncontrolled hypertension.

References
