Pulse Pressure and Mean Arterial Pressure in Relation to Ischemic Stroke Among Patients With Uncontrolled Hypertension in Rural Areas of China

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Background and Purpose—Information has been sparse on the comparison of pulse pressure (PP) and mean arterial pressure (MAP) in relation to ischemic stroke among patients with uncontrolled hypertension. The present study examined the relation among PP, MAP, and ischemic stroke in uncontrolled hypertensive subjects in China.

Methods—A total of 6104 uncontrolled hypertensive subjects aged ≥35 years were screened with a stratified cluster multistage sampling scheme in Fuxin county of Liaoning province of China, of which 317 had ischemic stroke.

Results—After multivariable adjustment for age, gender, and other confounders, individuals with the highest quartile of PP and MAP had ORs for ischemic stroke of 1.479 (95% CI: 1.027 to 2.130) and 2.000 (95% CI: 1.373 to 2.914) with the lowest quartile as the reference. Adjusted ORs for ischemic stroke were 1.306 for MAP and 1.118 for PP with an increment of 1 SD, respectively. Ischemic stroke prediction of PP was annihilated when PP and MAP were entered in a single model. In patients aged <65 years, on a continuous scale using receive operating characteristics curve, ischemic stroke was predicted by PP (P<0.001) and MAP (P<0.001). The area under the curve of PP (0.570, 95% CI: 0.531 to 0.609) differed from the area under the curve of MAP (0.633, 95% CI: 0.597 to 0.669; P<0.05). Among patients aged ≥65 years, presence of ischemic stroke was only predicted by MAP.

Conclusion—PP and MAP were both associated with ischemic stroke. Ischemic stroke prediction of PP depended on MAP. On a continuous scale, MAP better predicted ischemic stroke than PP did in diagnostic accuracy. (Stroke. 2008;39: 1932-1937.)

Key Words: hypertension ■ ischemic stroke ■ mean arterial pressure ■ pulse pressure

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 the 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; whereas results form some epidemiological studies indicate that PP is a better predictor of fatal stroke than MAP.⁷ In summary, there is controversy about the role of PP on stroke and which is better associated with stroke, MAP or PP, remains unclear.

The present study examined the relation among PP, MAP, and ischemic stroke in uncontrolled hypertensive subjects. For this purpose, we studied 6104 randomly selected uncontrolled hypertensive subjects aged ≥35 years from Liaoning province of China.

Subjects and Methods

Study Population
This is a large-scale cross-sectional study. The procedures followed were in accordance with ethical standards of the responsible committee on human experimentation of China Medical University. Informed consent was obtained from all subjects. The study was conducted from October 2004 to June 2006 in a rural community of Liaoning province, China. The study used a stratified cluster, multistage sampling method, which included samples from uncontrolled hypertensives in the northern, southern, western, eastern, and...
central regions of Fuxin county in Liaoning province. Only one small town was selected from each region. Finally, 10 rural villages near each small town were randomly selected from different geographic areas. In total, 5 small towns from these regions and 30 rural villages were selected to a resident group aged ≥35 years and Han and Mongolia ethnicities were the main ethnic groups included. A total of 7592 patients with uncontrolled hypertension were selected from these sampling units in rural areas. A total of 6104 uncontrolled hypertensive subjects (2675 men, 3429 women) aged ≥35 years were recruited in the study. The response rate was 80.4%. Secondary hypertensions were excluded.

Lifestyle Factors and Anthropometric and Laboratory Measurements

All surveys were conducted by local trained doctors using home visits. During the interview and examination, doctors administered a standard questionnaire including questions related to lifestyle factors. Data on demographic variables (age, gender, and race), smoking status, use of alcohol, and different classes of antihypertensive medication were obtained by interview. Drinking status was assessed by alcohol consumption; alcohol consumption was defined as the weekly consumption of beer, wine, and hard liquor converted in grams of alcohol. Current drinking was defined as alcohol consumption (≥8 g/week).9 Current smoking was defined as people who smoked at least one cigarette everyday and continued for at least 1 year. Smoking was assessed as part of the questionnaire. The individuals were asked whether or not they currently smoked ("Do you smoke currently?").

Body weight and height were measured with subjects wearing light clothing and without shoes. Body mass index was calculated by the weight in kilograms divided by height in square meters. BP was measured with a checked electronic sphygmomanometer (Omron; Dalian, Liaoning, China), which had already been validated by the British Hypertension Society protocol.10 BP was measured 3 times in the sitting position for ≥5 minutes, and the mean value of the 3 separate SBP and 3 separate DBP measurements were used to determine the reported BP for that examination. Pulse rate was also collected with the electric sphygmomanometer.

Subjects were asked to fast for at least 12 hours before blood collection. Blood samples were obtained from an antecubital vein into Vacutainer tubes containing EDTA. Blood chemical analyses were performed at a central, certified laboratory. Serum glucose, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides were analyzed enzymatically on an Olympus AU640 autoanalyzer (Olympus, Kobe, Japan).

Definitions

Ischemic stroke was collected with an epidemiological questionnaire. Ischemic stroke was defined as a history of cerebrovascular events, which was documented by either cranial CT or MR scan (within the past 24 months before inclusion).

Uncontrolled hypertension was defined as SBP ≥140 mm Hg or DBP ≥90 mm Hg regardless of receiving antihypertensive medication. PP was calculated as the difference between SBP and DBP. MAP was calculated as DBP plus one third times (SBP minus DBP).

Statistical Analysis

Continuous variables were given as mean ± SD and categorical variables as percentage in each subgroup. Student t test and the χ² test were used to compare continuous and categorical differences, respectively. Prevalence of ischemic stroke by quartiles of PP and MAP was calculated and tested by P trend χ² test. PP and MAP were separately tested in a logistic regression model with the 2 variables on a continuous scale with results expressed as an OR for ischemic stroke as a function of 1-SD increase on the continuous scale. PP and MAP were also both divided into quartiles (MAP: <108 mm Hg, 108 to 117 mm Hg, 118 to 127 mm Hg, and >127 mm Hg, respectively; PP: <51 mm Hg, 51 to 65 mm Hg, 66 to 80 mm Hg, and >80 mm Hg, respectively) and the lowest quartiles chosen as reference in a logistic regression model. Another logistic regression model included PP and MAP simultaneously to assess relationships with adjustment for each other. Logistic regression models were adjusted for age and gender or multivariable for age, gender, body mass index, pulse rate, smoking, drinking alcohol, serum glucose, total cholesterol, LDL-C, HDL-C, triglycerides, and antihypertensive medication. Diagnostic accuracy of PP and MAP on a continuous scale in the prediction of ischemic stroke was estimated as the area under the curve (AUC) from receiver operating characteristic curves. The diagnostic accuracies were determined to evaluate the ability of the 2 parameters to correctly discriminate between individuals with and without ischemic stroke. Equality of the AUC on the receiver operating curves was tested using the algorithm suggested by Delong et al.11 All analyses were performed with SPSS statistical software version 12.0. A probability value less than 0.05 was accepted as indicating statistical significance.

Results

The present large-scale study of 6104 patients consisted of 56.2% females and mean age was 56 years (range, 35 to 92 years). The mean values of average SBP, DBP, PP, and MAP were 162.85 ± 22.69 mm Hg, 108.41 ± 12.53 mm Hg, and 56.2% females and mean age was 56 years (range, 35 to 92 years). The mean values of average SBP, DBP, PP, and MAP were 162.85 ± 22.69 mm Hg, 108.41 ± 12.53 mm Hg, and 118.41 ± 13.77 mm Hg, respectively.

The Table shows characteristics of the 6104 patients with uncontrolled hypertension. Of those, 317 had ischemic stroke, whereas 5787 were control subjects free of this disease. Meanwhile, there were 45 patients with coronary artery disease and 92 patients with hemorrhage stroke in this
selected population. As expected, patients with ischemic stroke had older age and higher levels of average SBP, DBP, PP, MAP, total cholesterol, LDL-C, and fasting glucose than patients without ischemic stroke (all \( P \leq 0.05 \)). Higher ratio of male gender and lower ratio of drinking alcohol were observed in patients with ischemic stroke (\( P \leq 0.01 \)). A total of 55.5\% patients with ischemic stroke and 21.1\% without ischemic stroke were receiving antihypertensive medication (\( P \leq 0.001 \)). There was no significant difference for pulse rate, body mass index, HDL-C, and triglycerides in patients with and without ischemic stroke (all \( P \leq 0.05 \)).

For product moment (Pearson) simple correlation, MAP was positively and significantly correlated with PP (\( P \leq 0.01 \)). The coefficients were 0.475 in patients aged \( \leq 65 \) years and 0.370 in patients aged \( >65 \) years, respectively. Figure 1 also showed that the mean level of PP was dramatically increased by quartiles of MAP (\( P \text{ trend} < 0.001 \)).

As shown in Figure 2, prevalence of ischemic stroke was increased by quartiles of MAP (2.96\%, 3.71\%, 7.06\%, and 7.67\%, respectively; \( P \text{ trend} < 0.001 \)) and by quartiles of PP (3.72\%, 4.57\%, 5.78\%, and 7.10\%, respectively; \( P \text{ trend} < 0.001 \)). Figure 3 shows the OR and 95\% CI for ischemic stroke as a function of quartiles of MAP and PP. After adjustment for gender and age, patients with MAP of \( >127 \) mm Hg and 118 to 127 mm Hg versus \( <108 \) mm Hg had ORs for ischemic stroke of 2.753 (95\% CI: 1.920 to 3.947) and 2.456 (95\% CI: 1.714 to 3.519), respectively. After multivariable adjustment, MAP of \( >127 \) mm Hg and 118 to 127 mm Hg versus \( <108 \) mm Hg had ORs for ischemic stroke of 2.000 (95\% CI: 1.372 to 2.888), respectively. Quartiles of PP were also associated with ischemic stroke. Patients with PP of \( >80 \) mm Hg versus \( <51 \) mm Hg had ORs for ischemic stroke of 1.508 (95\% CI: 1.049 to 2.168) after adjustment for gender and age and 1.479 (95\% CI: 1.027 to 2.130) after multivariable adjustment.

PP and MAP were also considered separately on a continuous scale in a logistic regression model; an increment of 1-SD in MAP was associated with an OR of 1.410 (95\% CI: 1.280 to 1.553) for ischemic stroke after adjustment for gender and age and 1.306 (95\% CI: 1.176 to 1.450) after multivariable adjustment. PP with a level greater by 1 SD had ORs of 1.140 (95\% CI: 1.018 to 1.027) for ischemic stroke after adjustment for gender and age and 1.118 (95\% CI: 1.007 to 1.264) after multivariable adjustment.

When PP and MAP were included in the same model as a continuous variable, ischemic stroke prediction of PP was annihilated (OR: 0.951, 95\% CI: 0.839 to 1.077) and MAP was continuously associated with ischemic stroke (OR: 1.348, 95\% CI: 1.201 to 1.514) after multivariable adjustment. Similar results were found for quartiles of MAP and PP (data not shown). Moreover, a 1-SD increment of age and LDL-C had ORs of 1.412 (95\% CI: 1.245 to 1.602) and 1.414 (95\% CI: 1.123 to 1.780) for ischemic stroke after multivariable adjustment.

As shown in Figure 4, in patients aged \( \leq 65 \) years, presence of ischemic stroke was predicted by MAP (AUC: 0.633, 95\% CI: 0.597 to 0.669; \( P \text{ trend} < 0.001 \)) and PP (AUC: 0.693, 95\% CI: 0.630 to 0.756; \( P \text{ trend} < 0.001 \)) on a continuous scale using receiver operating characteristics curves.
curacy to identify patients with ischemic stroke for MAP and PP over the entire continuous scale differed (AUC\textsubscript{1} versus AUC\textsubscript{2}, \(P<0.05\); Figure 4A). However, presence of ischemic stroke was predicted only by MAP (AUC: 0.592, 95% CI: 0.536 to 0.649; \(P=0.001\)), not by PP (AUC: 0.526, 95% CI: 0.469 to 0.583; \(P=0.352\)) among patients with uncontrolled hypertension aged \(\geq 65\) years (Figure 4B).

**Discussion**

This is, to our knowledge, the first study to compare the prognostic importance of PP and MAP on ischemic stroke in a rather large group of uncontrolled hypertensive subjects in China. In this present study, we demonstrated that PP and MAP were both associated with ischemic stroke in uncontrolled hypertensive individuals. Ischemic stroke prediction of PP depended on MAP. On a continuous scale, MAP better predicted ischemic stroke than PP in diagnostic accuracy.

This is not a conventional epidemiological study searching for causal factors for ischemic stroke. The focus of this article was instead to examine the ability of PP and MAP to identify patients among uncontrolled hypertensive subjects with ischemic stroke. 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 pulse rate.\textsuperscript{12,13} The steady component, estimated by MAP, is a function of left ventricular contractility, pulse rate, and vascular resistance and elasticity averaged over time.\textsuperscript{14} In the present study, elevated MAP level was independently associated with ischemic stroke, which was similar to other studies.\textsuperscript{5–8} We demonstrated an increased OR for ischemic stroke as a function of MAP in quartiles or on a continuous scale.

In the present study, prevalence of ischemic stroke was increased with quartiles of PP (\(P\) trend <0.001). Patients with PP of \(>80\) mm Hg versus \(<51\) mm Hg had an OR for ischemic stroke of 1.508 (95% CI: 1.049 to 2.168). The association was consistent after multivariable adjustment. PP was associated with ischemic stroke in uncontrolled hypertensive subjects, which was not similar to other results.\textsuperscript{5,15–17} However, ischemic stroke prediction of PP was annihilated when entered with MAP in the same model, which was similar to another study in Japan.\textsuperscript{18} The result indicated that ischemic stroke prediction of PP depended on MAP, not associated with ischemic independently of MAP. Correlation between PP and MAP also indirectly proved the point. Physiologically speaking, 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.\textsuperscript{1} This approach may explain why, in a large population with a given genetic and environmental background,\textsuperscript{19} 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 cardiovascular morbidity and mortality. Rizzoni et al\textsuperscript{20} proved that structural alterations of small artery walls are a significant cardiovascular risk factor in hypertensive subjects, but in association with increased PP.

In our study, antihypertensive medication was positively associated with ischemic stroke after multivariable adjustment. Similar results were observed when different classes of antihypertensive drug treatments were simultaneously ad-
justed in a single model. A possible reason was that only the subjects who had cardiovascular or cerebrovascular disease were positively receiving antihypertensive medication in the rural community. Relationships between different classes of antihypertensive treatment and ischemic stroke should be further investigated in prospective studies.

In addition, when evaluated using receiver operating characteristic curves, MAP had some diagnostic ability for ischemic in middle-aged and older patients. However, PP in patients aged <65 years, not in patients aged ≥65 years, had some diagnostic ability for ischemic stroke. Limited statistical power and antihypertensive medication use might partly

**Figure 4.** A, Diagnostic accuracy of PP and MAP on a continuous scale in the prediction of ischemic stroke using receiver operating characteristic curve in patients aged <65 years. B, Diagnostic accuracy of PP and MAP on a continuous scale in the prediction of ischemic stroke using receiver operating characteristic curve with in patients aged ≥65 years. AUC with 95% CI is noted under each curve; probability value is for testing diagnostic accuracy against the null hypothesis. Comparison between the AUCs is noted in the bottom panel.
explain this lack of association. Despite this, MAP had better diagnostic ability for ischemic stroke than PP. 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 brainstem, 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. 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, lead to a progressive underestimation of peripheral vascular resistance by the mean BP equation.

Data from Framingham suggest that antihypertensive treatment may not confound the association between BP and coronary heart disease. Moreover, hypertension and ischemic stroke are prevalent in rural areas of China and the controlled rate of hypertension is very low. So we selected uncontrolled hypertensive subjects to supply a modest strategy to stroke detection in clinical therapy.

Some limitations should also be considered in light of these results. First, the major limitation of the present study is that it is cross-sectional, and thus patients with ischemic stroke are identified retrospectively. Correspondingly, risk factors were not independent of outcome, ie, smoking and drinking habits are likely to have changed occurrence of the event. It should be distinguished in some prospective studies. Second, there is less significant power to compare the relation between calculated BP components and coronary artery disease because of few patients in the present study. Third, the patients with ischemic stroke we observed were nonfatal stroke, not including fatal stroke, may be a selection bias.

Summary

In conclusion, the present study examined the ability of PP and MAP to diagnose individuals with ischemic stroke in uncontrolled hypertensive subjects. PP and MAP were both associated with ischemic stroke in uncontrolled hypertensive individuals in rural areas of China. Ischemic stroke prediction of PP depended on MAP. On a continuous scale, MAP better predicted ischemic stroke than PP in diagnostic accuracy.

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Disclosures

None.

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