Association of Blood Pressure Indices and Stroke Mortality in Isolated Systolic Hypertension

Furcy Paultre, PhD; Lori Mosca, MD, PhD

Background and Purpose—Isolated systolic hypertension (ISH), systolic blood pressure (BP) >160 mm Hg and diastolic BP (DBP) <90 mm Hg, is associated with stroke; however, the correlation between specific BP indices and stroke mortality in ISH is not defined.

Methods—In a pooled analysis of 9 epidemiological studies, we examined whether pulse pressure (PP) was more predictive of stroke mortality than systolic BP (SBP), DBP, or mean BP (MAP) in persons with ISH. Subjects (n=682; 29% male; 77% white; mean age 63.6 years) with ISH, free of cardiovascular disease, and not on antihypertensive drug therapy at baseline were followed a mean of 13.0±7.3 years, and 54 stroke deaths occurred. The relative importance of each BP index was compared by the decrease in the −2 log likelihood (a measure of model agreement with data) because of the addition of 1 or a combination of BP indices to a Cox regression model. Hazards ratios (HRs) for fatal stroke for a 1-SD in BP index were determined.

Results—PP was the best predictor of stroke mortality based on the decrease in the −2 log likelihood (10.65; P=0.001; HR=1.52), followed by SBP (7.19; P=0.007; HR=1.40), DBP (2.76; P=0.10; HR=0.80), or MAP (0.39; P=0.39; HR=1.10). Any combination of BP indices did not exceed a decrease in the −2 log likelihood of 10.72.

Conclusion—These data suggest that in persons with ISH, PP is a better predictor of fatal stroke than SBP, DBP, or MAP.

Key Words: blood pressure ■ hypertension ■ stroke

Isolated systolic hypertension (ISH) is characterized by elevated systolic blood pressure (BP) in the presence of normal diastolic BP (DBP). A number of studies, including the Systolic Hypertension in the Elderly Program (SHEP), have defined ISH as systolic BP (SBP) >160 mm Hg and DBP <90 mm Hg.1 Prevalence of ISH increases with age and is associated with increased arterial stiffness. Large-artery stiffness increases in middle-aged and elderly persons,2 which causes an increase in SBP and a decrease in DBP.3 This results in an increase in pulse pressure (PP; SBP−DBP) and a higher prevalence of ISH in many older individuals.4 Epidemiological studies have demonstrated that persons with ISH are at increased risk of stroke.1 It remains unclear which of the commonly used BP indices best predicts stroke in persons with ISH.

Methods
Data were pooled from 9 long-term epidemiological cohort studies based in the United States as described previously.5 Individuals were included in this study if at baseline they were ≥30 years of age, were free of cardiovascular disease, met the criteria for ISH, and were not on antihypertensive drug therapy. Stroke mortality was defined by International Classification of Diseases (ICD) codes 430 to 438, which included hemorrhagic and nonhemorrhagic events. Mean BP (MAP) was approximated by (SBP+2DBP)/3. Cox proportional hazards regression was used to compare the association between BP indices and stroke mortality. The relative importance of BP indices was compared by the decrease in the −2 log likelihood statistic because of the addition of the individual or dual BP indices to the model adjusted for baseline values of age, gender, ethnicity, cigarette smoking, diabetes, cholesterol, and body mass index.6

Results
At baseline, 682 subjects (29% male; 77% white) with a mean age of 63.6±8.9 years met the criteria for ISH. During a mean follow-up time of 13.0±7.3 years, 54 stroke deaths were observed.

PP was more predictive of stroke mortality than SBP, DBP, or MAP. Decrease in the −2 log likelihood statistic with the addition of a single BP index (df=1) to the model was greater for PP (10.65; P=0.001) than for SBP (7.19; P=0.007), DBP (2.76; P=0.10), or MAP (0.39; P=0.39; Figure 1). The magnitude of the percent change in risk of hazard of stroke mortality for a 1-SD increase in BP was also greater and more significant for PP (52%; P=0.0002) than for SBP (40%; P=0.004), DBP (−20%; P=0.065), or MAP (10%; P=0.53; Table).

Because all 4 BP indices are linear combinations of each other, ≤2 can be used additively in a model. The decrease in
the $-2\log$ likelihood statistic when any 2 BP indices (ie, SBP–DBP, SBP–PP, SBP–MAP, DBP–PP, DBP–MAP, or PP–MAP) were added to the multivariable Cox model was 10.72 (df = 2; $P = 0.005$; Figure 1). This is the maximum decrease in the $-2\log$ likelihood statistic attributable to any additive combination of these 4 BP indices. PP alone accounted for 99% (10.65 (PP)/10.72 (2BP)) of the total possible decrease of the $-2\log$ likelihood statistic attributable to any additive combination of BP indices.

We further examined models containing 2 BP indices. MAP was excluded because of its weak association. Because the decrease in the $-2\log$ likelihood statistic attributable to any 2 BP indices was 10.72 (2BP), the decrease attributable to the addition of a second BP index to a model containing a different initial BP index was the difference between 10.72 (2BP) and the initial decrease attributable to the first BP index. Therefore, the $-2\log$ likelihood was decreased to 7.96 (10.72 (2BP)–2.76 (DBP); $P = 0.005$) by the addition of SBP to a model containing DBP and to a similar order of magnitude, 3.53 (10.72 (2BP)–7.19 (SBP); $P = 0.06$), when DBP was added to a model containing SBP (model 1). In contrast, the decrease in the $-2\log$ likelihood when PP was added to a model containing SBP (3.53 [10.72 (2BP)–7.19 (SBP); $P = 0.06$] was 50× larger than when SBP was added to a model containing PP (0.07 [10.72 (2BP)–10.65 (PP)], $P = 0.79$; model 2, Figure 2A).

Similarly, the decrease in the $-2\log$ likelihood was again much larger (112×) when PP was added to a model containing DBP (7.96 [10.72 (2BP)–2.76 (DBP); $P = 0.005$]) than when DBP was added to a model containing PP (0.07 [10.72 (2BP)–10.65 (PP)]; $P = 0.79$; model 3, Figure 2B).

**Discussion**

Our main finding was that PP was more predictive of stroke mortality than SBP, DBP, or MAP in of individuals with ISH. In our study, SBP (positively) and DBP (negatively) were significantly associated with stroke mortality when considered separately.

With increased peripheral resistance, increased cardiac output, or both, which begins sometimes in young individuals and often in aging subjects, SBP and DBP rise progressively with age.\(^3\) In contrast, because large-artery stiffness increases in middle-aged and elderly individuals,\(^2\) SBP rises but DBP falls, resulting in an increased PP, often with preservation of MAP in a stable, normal level.\(^3\) An increase in SBP with fixed DBP and a decrease in DBP with fixed SBP occur solely with an increase in PP. These findings imply that in persons with ISH, stroke mortality is more related to increased large-artery stiffness than to increased peripheral vascular resistance. These analyses may be more relevant to ischemic rather than cerebral hemorrhagic stroke. A major limitation of this study was the lack of knowledge about treatment of systolic hypertension during follow-up. Our data suggest that stroke mortality is more related to the

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**Table 1. Cox Proportional Models Relating Stroke Mortality to BP Indices**

<table>
<thead>
<tr>
<th>BP Variable</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single BP components</td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>1.40 (1.12–1.76)</td>
</tr>
<tr>
<td>DBP</td>
<td>0.80 (0.63–1.01)</td>
</tr>
<tr>
<td>PP</td>
<td>1.52 (1.22–1.91)</td>
</tr>
<tr>
<td>MAP</td>
<td>1.10 (0.82–1.47)</td>
</tr>
<tr>
<td>Dual BP components</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>1.42 (1.14–1.77)</td>
</tr>
<tr>
<td>DBP</td>
<td>0.79 (0.63–0.98)</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
</tr>
<tr>
<td>PP</td>
<td>1.61 (1.04–2.49)</td>
</tr>
<tr>
<td>SBP</td>
<td>0.94 (0.61–1.46)</td>
</tr>
<tr>
<td>Model 3</td>
<td></td>
</tr>
<tr>
<td>PP</td>
<td>1.50 (1.16–1.94)</td>
</tr>
<tr>
<td>DBP</td>
<td>0.97 (0.75–1.25)</td>
</tr>
</tbody>
</table>

PP, SBP, DBP, or MAP and their 95% CI.

*1-SD unit change.
†Adjusted for age, gender, cigarette smoking, diabetes, cholesterol, and body mass index.
pulsatile component, a marker for large-artery stiffness, rather than the steady component, which reflects peripheral resistance, of BP.

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References
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