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 for 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 statistic with the model added. The decrease in PP was compared to the decrease in −2 log likelihood statistic with the model added 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—PP was the best predictor of stroke mortality based on the decrease in the −2 log likelihood statistic (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 statistic 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 the 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 (10.65pp; P=0.001) than for SBP (7.19sbp; P=0.007), DBP (2.76dbp; P=0.10), or MAP (0.39map; P=0.39; Figure 1). The magnitude of the percent change in risk 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, DPBP−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 in the MAP was excluded because of its weak association. Because the decrease in the MAP was much larger (112) when PP 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 DBP (3.53 [10.72−7.19]; P=0.06) was 50× larger than when SBP was added to a model containing PP (0.07 [10.72−10.65]; 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 [10.72−2.76]; P=0.005) than when DBP was added to a model containing PP (0.07 [10.72−10.65]; P=0.79; model 3, Figure 2B).

**Figure 1.** Decrease in the −2 log likelihood when a single BP index (PP [P=0.001], SBP [P=0.007], DBP [P=0.10], or MAP [P=0.53]) or a combination of any 2 BP indices (P=0.005) was added to a Cox proportional hazards regression model predicting stroke mortality adjusted for age, gender, ethnicity, cigarette smoking, diabetes, cholesterol, and body mass index.

**Figure 2.** Decrease in the −2 log likelihood when adding SBP to model that contains PP and vice versa (A; model 2) and adding DBP to model that contains PP and vice versa (B; model 3), in a Cox proportional hazards regression model predicting stroke mortality adjusted for age, gender, ethnicity, cigarette smoking, diabetes, cholesterol, and body mass index.

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. In contrast, because large-artery stiffness increases in middle-aged and elderly individuals, SBP rises but DBP falls, resulting in an increased PP, often with preservation of MAP in a stable, normal level. 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

<table>
<thead>
<tr>
<th>BP Variable Relating Stroke Mortality to BP Indices*</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single BP components</strong></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><strong>Dual BP components</strong></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>

*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.

Acknowledgments

This study was supported by a grant from the National Heart, Lung and Blood Institute (K08 HL 03681) and by a grant from the American Heart Association (9750703N). The authors would like to thank the steering committee members of the Women’s Pooling Project for their participation in the project, including Ralph D’Agostino, Boston University; Elizabeth Barrett-Connor, University of California San Diego; Victor Hawthorne, University of Michigan; Millicent Higgins, University of Michigan; William Kannel, Framingham Study; Julian Keil, Medical University of South Carolina; Michael Stern, University of Texas, University of Maryland School of Medicine; Susan Sutherland, Research Institute at Mission St. Joseph’s; H. Al Tyroler, University of North Carolina; and Aaron Folson, University of Minnesota.

References

Association of Blood Pressure Indices and Stroke Mortality in Isolated Systolic Hypertension
Furcy Paultre and Lori Mosca

Stroke. 2005;36:1288-1290; originally published online May 5, 2005;
doi: 10.1161/01.STR.0000166201.79222.4d
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/36/6/1288

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/