Four-Limb Blood Pressure as Predictors of Mortality in Elderly Chinese

Chang-Sheng Sheng, Ming Liu, Wei-Fang Zeng, Qi-Fang Huang, Yan Li, Ji-Guang Wang

See Editorial Commentary, pp 1146–1147

Abstract—The predictive value of blood pressure (BP) for cardiovascular morbidity and mortality diminishes in the elderly, which may be confounded and compensated by the BP differences across the 4 limbs, markers of peripheral arterial disease. In a prospective elderly (≥60 years) Chinese study, we performed simultaneous 4-limb BP measurement using an oscillometric device in the supine position, and calculated BP differences between the 4 limbs. At baseline, the mean age of the 3133 participants (1383 men) was 69 years. During 4 years (median) of follow-up, all-cause and cardiovascular deaths occurred in 203 and 93 subjects, respectively. In multiple regression analyses, arm BPs on the higher arm side of systolic BP did not predict mortality (P=0.06) except for a negative association between mean arterial pressure and total mortality (P=0.04). However, in adjusted analyses, the hazard ratios associated with a 1-SD decrease in ankle-brachial BP index or increase in interarm or interankle BP difference were 1.15 to 1.23 for total mortality (P≤0.01) and 1.17 to 1.24 for cardiovascular mortality (P≤0.04). In categorical analyses, similar results were observed for a decreased ankle-brachial index (≤0.90, ≤0.95, or ≤1.00) or increased interarm or interankle difference (≥15 mm Hg or ≥10 mm Hg). In conclusion, in the elderly, above and beyond arm BP level and together with ankle-brachial index, the interarm and interankle BP differences improve prediction of mortality. Simultaneous 4-limb BP measurement has become feasible with current technology and might be useful in cardiovascular prevention. (Hypertension. 2013;61:1155-1160.)

Key Words: ankle-brachial index ■ Chinese ■ elderly ■ interankle blood pressure difference ■ interarm blood pressure difference ■ mortality

High blood pressure (BP) is an established modifiable risk factor for cardiovascular disease and mortality. However, the association between BP and cardiovascular risk weakens in the elderly.1 A major confounding factor is atherosclerotic peripheral arterial disease (PAD).2,3 When PAD is present in subclavian and brachial arteries, arm BP cannot be accurately measured, and hypertension therefore cannot be timely diagnosed and properly managed in clinical practice.4,5

Current technology allows simultaneous BP measurement in 4 limbs,6,7 which may provide a comprehensive evaluation of BP and generate accurate BP differences between 4 limbs, such as ankle-brachial BP index (ABI) and the interarm and interankle BP differences. ABI is a well-documented diagnostic tool for PAD in lower extremities.8,9 The interarm BP difference is also being recognized as an indicator of PAD in the subclavian or brachial arteries.2,5,8-11 To the best of our knowledge, the diagnostic and prognostic significances of the interankle BP difference have not been investigated in prospective studies.

We performed simultaneous BP measurement in 4 limbs in an elderly Chinese population, which was prospectively followed up for mortality. In the present study, we investigated total and cardiovascular mortality in relation to the level of arm BP, ABI, and the interarm and interankle BP differences.

Methods

Study Population

Our study was conducted in the framework of the Chronic Disease Detection and Management in the Elderly (260 years) Program supported by the municipal government of Shanghai. In a newly urbanized suburban town, 30 kilometers from the city center, we invited all residents of 60 years or older to take part in comprehensive examinations of cardiovascular disease and risk. The Ethics Committee of Ruijin Hospital, Shanghai Jiaotong University School of Medicine approved the study protocol. All subjects gave written informed consent.

A total of 3263 subjects (participation rate 90%) were enrolled in the period from 2006 to 2008, and followed up for vital status and cause of death till June 30, 2011. We excluded 130 subjects from the present analysis, because 4-limb BP measurement was not performed (n=45) or because of missing other information (n=85). Thus, the number of participants included in the present analysis was 3133.

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Hypertension is available at http://hyper.ahajournals.org DOI: 10.1161/HYPERTENSIONAHA.111.00969
Four-Limb BP Measurements

Four-limb BP was measured by the use of the Vascular Profiler-1000 device (Omron, Kyoto, Japan), which operates the oscillometric technique and has been validated previously.5,6 Trained technicians and physicians placed the pressure cuffs on both arms and both ankles and performed the measurements, after the subject had rested for ≥10 minutes in the supine position. The device simultaneously and automatically measures the BPs twice, and then discards the first measurement and only stores the second one in the database.

ABI was reported by the device as the ratio of the lower ankle over the higher brachial systolic BPs. For systolic and diastolic BPs separately, we calculated the interarm and interankle BP differences as the absolute value of the difference between the right and left brachial BPs and between the right and left ankle BPs, respectively. Pulse pressure was the difference between systolic and diastolic BPs. Mean arterial pressure was two-thirds diastolic pressure plus one-third systolic pressure.

Filed Work

One experienced physician measured each participant’s BP 3x consecutively using a validated Omron 7051 oscillometric BP monitor (Omron, Kyoto, Japan) on the nondominant arm, after the subjects had rested for ≥5 minutes in the sitting position. The same observer also administered a standardized questionnaire to collect information on medical history, lifestyle, and use of medications. Hypertension was defined as a sitting BP (average of 3 readings) of ≥140 mm Hg systolic or ≥90 mm Hg diastolic or as the use of antihypertensive drugs, unless the interarm difference of BP measured in the supine position was ≥10 mm Hg (n=285). In the latter case, hypertension was defined according to supine BP on the higher arm side and the same diagnostic thresholds. A trained technician performed anthropometric measurements. Venous blood samples were drawn after overnight fasting for the measurement of plasma glucose, serum total cholesterol, and triglycerides. Diabetes mellitus was defined as a plasma glucose concentration of ≥7.0 mmol/L fasting or 11.1 mmol/L at any time or as the use of antidiabetic agents.

During follow-up, information on vital status and the cause of death was obtained from the official death certificate, with further confirmation by the local Community Health Center and family members of the deceased people. The International Classification of Diseases 9th Revision was used to classify the cause of death. Cardiovascular mortality included deaths attributable to stroke, myocardial infarction, and other cardiovascular diseases.

Statistics

For database management and statistical analysis, we used SAS software (version 9.13, SAS Institute, Cary, NC). Means and proportions were compared with the Student t test and Fisher exact test, respectively. Multiple Cox regression analysis was performed to compute hazard ratios with their 95% confidence intervals (CIs). The log-rank test was used to compare the cumulative incidence of mortality between groups with Kaplan–Meier survival function to show the time to death. In continuous analyses, we analyzed the BP indexes for both systolic and diastolic BPs, except ABI that was only calculated for systolic BP. In categorical analyses, we defined reduced ABI (≤0.90,12 ≤0.95,13 or ≤1.0014) and increased interarm and interankle BP differences (≥15 mm Hg or ≥10 mm Hg) according to systolic BP only, and used various cutoff limits according to the current guidelines15 or otherwise the literature.3,9,10,11 We plotted time-dependent–operating characteristics curves and calculated the c statistic with CIs to examine the incremental prognostic value for mortality.12 We also evaluated the overall improvement in reclassification of subjects by the net reclassification improvement method.14

Results

Characteristics of the Study Participants

At baseline, the 3133 participants (1383 [44.1%] men) had a mean (±SD) age of 69.0±7.4 years and included 1895 (60.5%) and 285 (9.2%) patients with hypertension and diabetes mellitus, respectively. Table 1 shows the baseline characteristics by sex.

Continuous Analyses

During 4.0 years (median) of follow-up, the cumulated number of person-years was 12 800, and all-cause and cardiovascular deaths occurred in 203 and 93 subjects, respectively. In multiple Cox regression analyses adjusted for age, sex, body mass index, current smoking, alcohol intake, use of antihypertensive drugs, diabetes mellitus, and serum total cholesterol, brachial BP on the higher arm side of systolic BP did not predict mortality (P≥0.06) except for a negative association between mean arterial pressure and total mortality (P=0.04; Table S1 in the online-only Data Supplement). However, the BP ratios and differences across the 4 limbs significantly predicted total (P≤0.01) and cardiovascular mortality (P≤0.04; Table 2). The hazard ratios associated with each 1-SD decrease in ABI or increase in the interarm or interankle BP difference were 1.15 to 1.23 for total mortality and 1.17 to 1.24 for cardiovascular mortality.

Categorical Analyses

The categorical analyses showed a curvilinear relationship between the BP ratios and differences across the 4 limbs and mortality (Figure 1), with a significantly higher incidence rate of total mortality in the presence of a reduced ABI (≤0.90, ≤0.95, or ≤1.00) or greater interarm or interankle difference (≥10 mm Hg or ≥15 mm Hg; Figure 2). After adjustment for the abovementioned covariates and for the brachial BP, multiple Cox regression analyses were confirmatory (Table 3). The hazard ratios ranged from 1.52 to 2.47 for total mortality (P<0.0001–0.02) and from 1.45 to 2.12 for cardiovascular mortality (P values from 0.06 to 0.27).

C-Statistics and Reclassification Analyses

We calculated the c-statistic to estimate the incremental prognostic value of the interarm and interankle differences beyond an ABI of ≥0.90 (Table S2). An interankle BP difference of ≥15 mm Hg alone or in combination with an interarm BP difference of 15 mm Hg significantly (P<0.001) increased the prognostic value for total (c-statistic from 0.54 to 0.59 or to 0.60, respectively) and cardiovascular mortality (c-statistic from 0.56 to 0.62 or to 0.63, respectively). However, an interarm BP difference of ≥15 mm Hg alone did not increase the prognostic value (P≥0.46).

Reclassification analysis was confirmatory. Net reclassification improvement for an interankle BP difference of ≥15 mm Hg was significantly (P<0.001) positive for total (0.14; 95% CI, 0.08–0.20) and cardiovascular mortality (0.20; 95% CI, 0.10–0.30).

Sensitivity Analyses

After exclusion of 83 persons with an ABI of ≤0.90, we performed sensitivity analysis on the interarm and interankle systolic BP differences. Similar trends and size of estimations for association were observed. However, because of the substantial reduction in the number of deaths, the association remained statistically significant only for the interankle BP.
The prevalence of PAD in our current study is lower than that of several previous studies in Chinese populations and other populations. The diagnostic threshold of ABI for the diagnosis of PAD might be an explanation. The Chinese might require a higher threshold of ABI, for example, 0.95 instead of 0.90.13 The oscillometrically measured ABI might also require a higher threshold, for example, 1.00 instead of 0.90.14 The prevalence of the interarm BP difference of 10 or 15 mm Hg was associated with a 60.0% and 70% increase in total and cardiovascular mortality, respectively.9 Similarly, in a pooled analysis of 11 studies based on individual data, an ABI of ≤0.90 was associated with a 60.0% and a 96% increase in total and cardiovascular mortality, respectively.19 In a Chinese study of patients with coronary heart disease, stroke, end-stage renal disease, or diabetes mellitus, an ABI of ≤0.90 was associated with a 53.4% and a 103.1% increase in total and cardiovascular mortality, respectively.20

Our study is the first Chinese population-based prospective study on the prognostic value of the interarm BP difference and ABI for mortality. Our finding is in line with the results of recent meta-analyses8,19 and the study of a cohort of Chinese patients.20 In a meta-analysis of 4 studies, an interarm BP difference of ≥15 mm Hg was associated with a 60.0% and 70% increase in total and cardiovascular mortality, respectively.9 Similarly, in a pooled analysis of 11 studies based on individual data, an ABI of ≤0.90 was associated with a 60.0% and a 96% increase in total and cardiovascular mortality, respectively.19 In a Chinese study of patients with coronary heart disease, stroke, end-stage renal disease, or diabetes mellitus, an ABI of ≤0.90 was associated with a 53.4% and a 103.1% increase in total and cardiovascular mortality, respectively.20

The prevalence of PAD in our current study is lower than that of several previous studies in Chinese and other populations. The diagnostic threshold of ABI for the diagnosis of PAD might be an explanation. The Chinese might require a higher threshold of ABI, for example, 0.95 instead of 0.90.13 The oscillometrically measured ABI might also require a higher threshold, for example, 1.00 instead of 0.90.14 The prevalence of the interarm BP difference of 10 or 15 mm Hg or more in our current research is also lower than that of other studies.19 Simultaneous measurement might have diminished the prevalence of the interarm and interankle BP differences. In addition to these technical explanations, ethnicity may play a role, especially when the known risk factors for PAD are considered.22 In our study, men had a much higher proportion of smokers but lower prevalence of reduced ABI than women, although men had slightly lower prevalence of diabetes mellitus.
Although the prognostic significance of ABI and the interarm and interankle BP differences are independent and additive, PAD can still be a common explanation of association. PAD, especially in the subclavian and brachial arteries, can also partially explain the diminished predictive value of the conventionally measured brachial BP in the elderly. When PAD is present in arteries in the upper extremities, the reduced BP on the diseased arm would not only possibly delay the diagnosis of hypertension, but also lead to inappropriate management of hypertension. Nonetheless, there is no direct radiological evidence for plaques in the interarm or interankle BP differences of 10 or 15 mm Hg or more. Imaging studies are required.

Our study should be interpreted within the context of its limitations. First, our study had a relatively short duration of follow-up and small number of events, which may compromise the quantitative accuracy of the studied associations. Second, the oscillometric technology, although validated in technological as well as outcome studies, might be still prone for measurement errors, especially in patients with incompressible arteries, and, depending on the level of ABI, might slightly differ from the manual Doppler technique in the measurement of ABI values. Moreover, this technology operates on a dedicated device, which is not cheap compared with existing equipments, such as the Doppler devices, and hence can be a barrier to its wide use as a clinical tool. Third, although we emphasize the importance of simultaneous measurement of 4-limb BPs, the clinically used 2-limb devices may be equally effective in the measurement of BP ratios or differences across the 4 limbs. Finally, a single measurement might be less accurate than multiple repeated measurements. Nonetheless, our previous reproducibility study has shown that as far as the BP ratio or difference is concerned, the inter-session variation is small.

In conclusion, in the elderly, the predictive value of the level of arm BP for mortality is limited. ABI provides additional predictive value. Above and beyond, the interarm and interankle BP differences improve prediction of mortality. Simultaneous 4-limb BP measurements have become feasible with current technology and might be useful in cardiovascular prevention, especially in the elderly.

Table 2. Continuous Analyses on the Prognostic Significance of Blood Pressure Ratio and Differences Across the 4 Limbs

<table>
<thead>
<tr>
<th>Blood Pressure Ratio or Difference</th>
<th>Total Mortality</th>
<th>Cardiovascular Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankle-brachial systolic blood pressure index, −0.09</td>
<td>1.22 (1.10–1.36) 0.0003</td>
<td>1.24 (1.07–1.44) 0.005</td>
</tr>
</tbody>
</table>

**Figure 1.** Incidence rate of total and cardiovascular mortality. Open and closed circles represent total and cardiovascular mortality, respectively, according to quartiles of ankle-brachial systolic blood pressure index (left) and the interarm (middle) and interankle systolic blood pressure differences (right). The number of deaths and subjects is given alongside the symbols and at the bottom, respectively. *P* values for trends of each group are given.

*Hazard ratios and their 95% confidence intervals were computed for each 1-SD decrease in ankle-brachial blood pressure index or increase in interarm and interankle blood pressure differences, with adjustments for age, sex, body mass index, current smoking, alcohol intake, use of antihypertensive drugs, diabetes mellitus, and serum total cholesterol.
Perspectives
In the elderly, PAD is prevalent. With increasing longevity, there would be a huge number of patients with this disease. Simultaneous 4-limb BP measurements may identify these patients, unidentified by the use of ABI alone, and hence might be used for the screening of patients with PAD. Nonetheless, imaging studies are required to investigate the arterial structural characteristics of patients with abnormal interarm or interankle BP differences.

Acknowledgments
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Table 3. Categorical Analyses on the Prognostic Significance of Blood Pressure Ratio and Differences Across the 4 Limbs

<table>
<thead>
<tr>
<th>Blood Pressure Ratio or Difference</th>
<th>Total Mortality</th>
<th>Cardiovascular Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Events/Patients on Risk (Rate per 1000 Person-years)</td>
<td>Hazard Ratio (95% Confidence Interval)*</td>
</tr>
<tr>
<td>Ankle-brachial systolic blood pressure index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.90 vs &gt;0.90</td>
<td>22/83 (65.9)</td>
<td>2.02 (1.24–3.30)</td>
</tr>
<tr>
<td>≤0.95 vs &gt;0.95</td>
<td>39/175 (55.8)</td>
<td>2.23 (1.52–3.26)</td>
</tr>
<tr>
<td>≤1.00 vs &gt;1.00</td>
<td>64/417 (15.3)</td>
<td>1.92 (1.39–2.66)</td>
</tr>
<tr>
<td>Interarm systolic blood pressure difference, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10 vs &lt;10</td>
<td>21/199 (25.5)</td>
<td>1.72 (1.06–2.80)</td>
</tr>
<tr>
<td>≥15 vs &lt;15</td>
<td>9/55 (40.3)</td>
<td>2.47 (1.24–4.93)</td>
</tr>
<tr>
<td>Interankle systolic blood pressure difference, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10 vs &lt;10</td>
<td>73/645 (28.1)</td>
<td>1.52 (1.16–2.06)</td>
</tr>
<tr>
<td>≥15 vs &lt;15</td>
<td>40/244 (41.8)</td>
<td>1.63 (1.12–2.38)</td>
</tr>
</tbody>
</table>

*Hazard ratios and their 95% confidence intervals were computed for patients at risk vs the rest of study participants in a Cox regression model adjusted for age, sex, body mass index, current smoking, alcohol intake, use of antihypertensive drugs, diabetes mellitus, serum total cholesterol, and arm systolic and diastolic blood pressures on the higher arm side of systolic blood pressure.
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Disclosures

J.-G. Wang reports receiving grants and lecture and consulting fees from Omron Healthcare (Kyoto, Japan). The other authors have no conflicts to report.

References

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Short title: Four-limb Blood Pressure and Mortality

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Fax: +86-21-64662193
Email: jiguangw@gmail.com
Table S1. Prognostic Significance of Arm Blood Pressure on the Higher Arm Side of Systolic Blood Pressure

<table>
<thead>
<tr>
<th>Blood pressure component, +1 SD</th>
<th>Total mortality</th>
<th></th>
<th>Cardiovascular mortality</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio (95% confidence interval)*</td>
<td>P value</td>
<td>Hazard ratio (95% confidence interval)*</td>
<td>P value</td>
</tr>
<tr>
<td>Systolic pressure, +19.6 mm Hg</td>
<td>1.04 (0.80-1.25)</td>
<td>0.71</td>
<td>1.11 (0.84-1.48)</td>
<td>0.46</td>
</tr>
<tr>
<td>Diastolic pressure, +10.1 mm Hg</td>
<td>0.81 (0.65-1.01)</td>
<td>0.06</td>
<td>0.78 (0.57-1.08)</td>
<td>0.13</td>
</tr>
<tr>
<td>Pulse pressure, +13.2 mm Hg</td>
<td>1.12 (0.94-1.33)</td>
<td>0.20</td>
<td>1.17 (0.91-1.51)</td>
<td>0.21</td>
</tr>
<tr>
<td>Mean arterial pressure, +12.5 mm Hg</td>
<td>0.80 (0.65-0.99)</td>
<td>0.04</td>
<td>0.80 (0.60-1.08)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

*Hazard ratios and their 95% confidence intervals were computed for each 1 standard deviation increase in systolic and diastolic blood pressures and pulse pressure and mean arterial pressure, respectively, in two separate Cox regression models adjusted for age, sex, body mass index, current smoking, alcohol intake, the use of antihypertensive drugs, diabetes mellitus, and serum total cholesterol.
Table S2. C-statistics Analysis on the Incremental Prognostic Value of the Inter-Arm and Inter-Ankle Blood Pressure Differences Beyond an Ankle-Brachial Index of 0.90 or Less

<table>
<thead>
<tr>
<th>Blood pressure ratio or difference</th>
<th>Total mortality</th>
<th></th>
<th></th>
<th>Cardiovascular mortality</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>c statistic</td>
<td>95% confidence interval</td>
<td>$P$ value*</td>
<td>c statistic</td>
<td>95% confidence interval</td>
<td>$P$ value*</td>
</tr>
<tr>
<td>Ankle-brachial index $\leq 0.90$</td>
<td>0.54</td>
<td>0.52-0.57</td>
<td>-</td>
<td>0.56</td>
<td>0.52-0.59</td>
<td>-</td>
</tr>
<tr>
<td>+Inter-arm blood pressure difference $\geq 15$ mm Hg</td>
<td>0.55</td>
<td>0.52-0.57</td>
<td>0.46</td>
<td>0.56</td>
<td>0.53-0.60</td>
<td>0.50</td>
</tr>
<tr>
<td>+Inter-ankle blood pressure difference $\geq 15$ mm Hg</td>
<td>0.59</td>
<td>0.56-0.62</td>
<td>$&lt;0.0001$</td>
<td>0.62</td>
<td>0.57-0.67</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>+Inter-arm blood pressure difference $\geq 15$ mm Hg and Inter-ankle blood pressure difference $\geq 15$ mm Hg</td>
<td>0.60</td>
<td>0.57-0.62</td>
<td>$&lt;0.0001$</td>
<td>0.63</td>
<td>0.58-0.67</td>
<td>$&lt;0.0001$</td>
</tr>
</tbody>
</table>

*For the comparison with the c-statistic of ABI$\leq 0.90$. 
Table S3. Sensitivity Analyses after Exclusion of 83 Subjects with an Ankle-Brachial Blood Pressure Index of 0.90 or Less

<table>
<thead>
<tr>
<th>Blood pressure difference</th>
<th>Total mortality</th>
<th></th>
<th>Cardiovascular mortality</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of events/patients on risk (rate per 1000 person-years)</td>
<td>Hazard ratio (95% confidence interval)*</td>
<td>P value</td>
<td>Number of events/patients on risk (rate per 1000 person-years)</td>
</tr>
<tr>
<td>Inter-arm systolic blood pressure difference, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10 vs &lt;10</td>
<td>13/175 (18.0)</td>
<td>1.44 (0.78-2.65)</td>
<td>0.24</td>
<td>5/175 (6.9)</td>
</tr>
<tr>
<td>≥15 vs &lt;15</td>
<td>4/41 (23.9)</td>
<td>2.04 (0.74-5.65)</td>
<td>0.17</td>
<td>2/41 (12.0)</td>
</tr>
<tr>
<td>Inter-ankle systolic blood pressure difference, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10 vs &lt;10</td>
<td>59/586 (25.8)</td>
<td>1.63 (1.17-2.27)</td>
<td>0.004</td>
<td>31/586 (13.5)</td>
</tr>
<tr>
<td>≥15 vs &lt;15</td>
<td>29/200 (37.9)</td>
<td>1.82 (1.18-2.80)</td>
<td>0.006</td>
<td>17/200 (22.2)</td>
</tr>
</tbody>
</table>

*Hazard ratios and their 95% confidence intervals were computed for patients at risk versus the rest of study participants in a Cox regression model adjusted for age, sex, body mass index, current smoking, alcohol intake, use of antihypertensive drugs, diabetes mellitus, serum total cholesterol, and arm systolic and diastolic blood pressures on the higher arm side of systolic blood pressure.