Prognostic Significance of Between-Arm Blood Pressure Differences

Rajiv Agarwal, Zerihun Bunaye, Dagim M. Bekele

Abstract—Blood pressure (BP) recordings often differ between arms, but the extent to which these differences are reproducible and whether the differences have prognostic importance is unknown. We enrolled 421 consecutive patients from a medicine and a renal clinic at a veterans' hospital. Three BP recordings were obtained in each arm using an oscillometric device in a sequential manner and repeated in 1 week. Patients were followed for all-cause mortality ≤7 years. The right arm had 5.1-mm Hg higher systolic BP that attenuated by ≈2.2 mm Hg a week later. Systolic BP dropped 6.9 mm Hg over 1 week and by an additional 5.3 mm Hg in patients with chronic kidney disease. Accounting for the visit and arm effect improved the reproducibility of the BP measurements. The intraclass correlation coefficient was 0.74, which improved to 0.88 after accounting for visit and 0.93 after accounting for arm. The crude mortality rate was 6.33 per 100 patient-years. Every 10-mm Hg difference in systolic BP between the arms conferred a mortality hazard of 1.24 (95% CI: 1.01 to 1.52) after adjusting for average systolic BP and chronic kidney disease. BP differences between arms are reproducible and carry prognostic information. Patients should have evaluation of BP in both arms at the screening visit. (Hypertension. 2008;51:657-662.)

Key Words: hypertension ▪ blood pressure measurement ▪ mortality ▪ cohort study ▪ survival analysis

Hypertension guidelines recommend that blood pressure (BP) should be assessed in both arms at the initial visit and the arm with the higher BP be used for BP assessment at subsequent visits. Several studies have pointed out that BPs differ between arms, with the right arm consistently reading higher by a small amount. The only study that examined the reproducibility of interarm differences concluded that the differences between arms were because of random variation and were consistent only when obstructive arterial disease was present. However, the latter study included only 2 patients with obstructive arterial disease.

People who have chronic kidney disease and those who are older are more likely to have obstructive arterial disease. Patients who have obstructive arterial disease are more likely to have greater reproducibility of between-arm BP differences. However, this notion of greater reproducibility of BP differences has never been examined in such a population. Furthermore, there are no data to support whether the simple measurement of BP difference between arms is of prognostic importance.

The objective of our study was to ascertain the reproducibility of BP differences between arms in a population known to have greater prevalence of obstructive arterial disease. Another aim was to assess the prognostic significance of the BP differences between arms.

Methods

Study Cohort

This was a prospective cohort study. Consecutive patients (n=423) were recruited from the renal clinic and a general medicine clinic of the Richard L. Roudebush Veterans’ Affairs (VA) Medical Center. Patients were excluded for body mass index >40 kg/m², acute renal failure, receiving renal replacement therapy, atrial fibrillation, or change in their antihypertensive drugs within 2 weeks of study enrollment. Chronic kidney disease (CKD) was defined as the presence of proteinuria on a spot urine specimen when the protein/creatinine ratio was ≥0.22 g/g or the estimated glomerular filtration rate was <60 mL/min per 1.73 m² by the 4-component Modification of Diet in Renal Disease formula: 186×Creatinine⁻⁰.⁷⁴×age⁻⁰.²⁰³×0.⁷⁴ if female and ×1.21 if black. Serum creatinine was not calibrated to Cleveland Clinic. Urine protein/creatinine ratio of >0.22 g/g correlates with urine protein excretion of >300 mg/d, the standard definition of clinical proteinuria. Accordingly, we selected this threshold of urine protein/creatinine ratio to reflect CKD.

The institutional review board of Indiana University and the research and development committee of the Richard L. Roudebush VA Medical Center approved this study, and all of the patients gave their written, informed consent.

BP Measurements

All of the measurements were recorded using the Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines by 1 nurse trained in the technique of BP measurement, using an appropriate cuff size

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with an oscillometric monitor with a manual inflator (Model HEM 412C, Omron Healthcare). Patients were seated for ≥5 minutes before measurements and refrained from smoking or caffeine ingestion for ≥30 minutes. The patient’s arm was kept at heart level during the measurement, and using an appropriate-sized cuff, 3 measurements were made. BP in each arm was measured in triplicate in no prespecified order but in a sequential manner. Measurements were repeated in both arms in triplicate at another clinic visit after 1 week. At least 30 seconds elapsed between BP measurements.

When any systolic BP differed by >25 mm Hg from the lowest recording in a consecutive set of 3 recordings in an arm or any diastolic BP differed from the lowest diastolic BP by >20 mm Hg, the recording was removed. Using these prespecified criteria, 185 recordings from 116 patients were removed. Of these, 99 systolic BP recordings were removed in 67 patients, and 97 diastolic BP recordings were removed from 71 patients.

**Ascertainment of Mortality**

The ascertainment of death was established using the computerized VA electronic medical chart system. The last date of visit to any VA facility was used to determine the last date of follow-up. In patients who were not seen at a VA facility in the previous 6 months, the Social Security Death Index was checked for mortality. Finally, the Renal Network, which keeps accurate records of all dialysis patients in the region, was contacted to assess vital status in those patients who were on dialysis but had not been seen recently (within 6 months) within the VA system.

**Statistical Analysis**

A linear mixed model with maximal likelihood estimation was used to analyze the data. These analyses take into account the correlated nature of the observations and missing data. BP over visits was modeled using random coefficients, with each subject having random intercepts and slopes over visits. An unstructured covariance matrix best described the data and was used. Arms were nested within subjects. The fixed effects tested were visits (baseline or 1 week), arm (right or left), and CKD (present or absent), as well as all of the interactions. The arm × CKD interaction and 3-way interactions were not significant and were removed from the final model. Model fit was tested using the likelihood ratio test, and no deterioration in model fit was noted after removal of these 2 terms.

Reproducibility was analyzed using a 4-level variance component model. Random intercepts were used for arms nested within visits, which, in turn, were nested within subjects. Thus BP measurements (level 1) would take on the same value for a given arm (level 2) across visits (level 3) or subjects (level 4) but would take on a unique value for a given combination of subject, visit, and arm. The interaction among subject, visit, and arm can be interpreted as a subject- and visit-specific bias of the arms. We compared the successively nested models with 2 levels (BP + subject), 3 levels (BP + subject + visit), and 4 levels (BP + subject + visit + arm) using the likelihood ratio test, and intraclass correlation coefficients were calculated (models A, B, and C, respectively, in Table 2).

Survival analyses were performed using the Cox model with the outcome of all-cause mortality. The baseline Cox model adjusted the absolute interarm difference at first visit with the average systolic BP at that visit (model A). Model B was further adjusted for CKD and model C for age. Proportionality assumption was tested by interact- ing the predictors with time and testing the model fit of the nested model by the likelihood ratio test and also by analyzing the Schoenfeld residuals. No evidence for nonproportionality of hazards was found. The functional form of the relationship between differences in BP between arms and outcome was analyzed using Martingale residuals.

All of the analyses were performed using Stata 10.0 (Stata Corp). P values were 2 sided and significance was set at 0.05.

**Results**

Between October 2000 and June 2002, 421 consecutive patients were recruited into the study and were followed up until September 2007. The trial flow is shown in Figure 1. Of these, 203 patients (48%) had no kidney disease and 218 (52%) had CKD. Approximately 72% of the patients returned for a follow-up visit at week 1. Baseline characteristics of the study sample are shown in Table 1. As expected, patients with CKD were older, had more diabetes mellitus, greater systolic BP, lower resting heart rate, greater antihypertensive drug use, more vascular disease, and there were less smokers.

Figure 2 shows the box plots of systolic and diastolic BP between arms, visits, and patients with and without CKD. The magnitude and direction of changes in BP are shown in Table 2. The right arm, on average, had 5.1-mm Hg higher systolic BP that attenuated by 2.2 mm Hg over the next visit. Systolic BP was higher in CKD patients by 11.6 mm Hg. Systolic BP dropped 6.9 mm Hg from the first to second visit and by an additional 5.3 mm Hg if patients had CKD. Thus, the visit effect was much more marked in CKD patients. Similar results were noted for diastolic BP, except that a trend toward lower diastolic BP was seen in patients with CKD. Patients with higher systolic BP had a fall in BP and those with lower BP had an increase in BP from the first visit to the next. Thus, the intercepts and slopes of BP were inversely related. Regression to the mean was also observed for diastolic BP.

At baseline visit, 252 patients (61%) had between-arm systolic BP difference within 10 mm Hg, 118 (29%) had difference between 10 and 20 mm Hg, and 40 (10%) had BP difference that exceeded 20 mm Hg. At week 1 visit, 214 (72%) had systolic BP difference within 10 mm Hg, 71 (24%) had difference between 10 and 20 mm Hg, and 12 (4%) had BP difference that exceeded 20 mm Hg. Diastolic BP differences between arms were within 5 mm Hg in 237 patients (58%), within 5 to 10 mm Hg in 113 patients (28%), and exceeded 10 mm Hg in 60 patients (15%) at visit 1. The corresponding differences at the week 1 visit were 67%, 26%, and 7%, respectively. Table 3 shows the SDs between subjects, visits, and arms and the of the residuals in successive models. The residual SD fell, and intraclass correlation coefficient improved with successive models accounting for the unique effects of visits and arms within individuals.
The median duration of follow-up was 5.6 years. A total of 131 (31%) patients died over 2068 years of cumulative follow-up, yielding a crude mortality rate of 6.33 per 100 patient-years. Table 4 shows the hazard ratio of increasing between-arm difference in systolic BP and all-cause mortality. For every 10-mm Hg increase in the difference between arms, mortality increased 28%. CKD was a potent risk factor for all-cause mortality, and even after adjusting
for CKD, the risk of between-arm differences on mortality persisted. Figure 3 shows the differences in mortality between patients with and without CKD. Nonetheless, increasing differences in systolic BP between arms were associated with increasing mortality regardless of the presence or absence of CKD. Age was correlated with CKD, BP, and between-arm BP differences. Although accounting for age removed the statistical significance of the between-arm BP difference on mortality (Table 4, model C), the directionality of the observations was intact.

**Discussion**

In this study we found that in veterans attending a renal clinic or a general medicine clinic, there were consistent differences in BP between arms. At each of the visits, ≈30% of the patients had between-arm systolic BP differences that exceeded 10 mm Hg, and between 30% and 40% of the patients had between-arm diastolic BP differences that exceeded 5 mm Hg. On average, the right arm had ≈5-mm Hg higher systolic BP that attenuated by ≈2 mm Hg a week later. Systolic BP dropped ≈7 mm Hg from over 1 week and by an additional ≈5 mm Hg in CKD patients. Accounting for the visit and arm effect reduced the residual variance and improved the reproducibility of the measurements. Finally, every 10-mm Hg difference in systolic BP conferred a 24% higher mortality hazard after accounting for average systolic BP at baseline and CKD.

Interarm BP differences have been evaluated by several investigators.2–11 The magnitude of the differences between arms has varied considerably between studies. For example, Singer and Hollander5 found systolic BP difference that exceeded 10 mm Hg in ≈40% of the patients, similar to our report. In contrast, Eguchi et al11 noted that 23% of the patients had interarm systolic BP differences that exceeded 5 mm Hg in each of the 2 days, but the differences diminished

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm</td>
<td>-5.1</td>
<td>-2.6</td>
</tr>
<tr>
<td>Visits</td>
<td>-6.9</td>
<td>-5.1</td>
</tr>
<tr>
<td>CKD</td>
<td>11.6</td>
<td>-1.9</td>
</tr>
<tr>
<td>Arm×visits</td>
<td>2.2</td>
<td>1.1</td>
</tr>
<tr>
<td>visits×CKD</td>
<td>-5.3</td>
<td>-3.4</td>
</tr>
<tr>
<td>Constant</td>
<td>144</td>
<td>86.4</td>
</tr>
</tbody>
</table>

Arm×CKD and the 3-way interaction were not significant and were removed from the model.

Figure 2. Box plot of systolic BP among arms, visits, and presence and absence of CKD. The middle bar represents the median, and the box represents the 75th and 25th percentile. The upper whisker is the third quartile+1.5×interquartile range. The lower whisker is the first quartile−1.5×interquartile range. The estimates of differences among arms, visits, and CKD are shown in Table 2.
as the number of BP readings increased. Other studies have shown 10% to 20% prevalence of systolic BP interarm differences of ≥10 mm Hg.2–4 Sequential measurements reveal a slightly higher BP difference compared with the simultaneous method.11

We observed a significant regression of BP to the mean in our patients. Those patients who had BP that was high initially had fall in BP and vice versa. These effects were more pronounced in patients with CKD. Regression to the mean has been reported previously in patients with essential hypertension; however, patients with CKD appeared to have a greater regression to the mean.16 Although we did not specifically examine the mechanism of regression to the mean in CKD patients, it is well recognized that patients with CKD have a heightened state of sympathetic activation.17 This activation may subside from one visit to the next and lead to a greater fall in BP, as we observed in our sample.

The consistency of between-visit differences in BP has been evaluated by only 1 study.11 A significant correlation in BP differences between arms from visit to visit was noted. However, on repeating the BP measurements at the same visit, the differences diminished and were no longer statistically significant. This led the authors to conclude that the differences between arms were because of random variation.11 In contrast to their study, our patients had CKD, more diabetes, vascular disease, and were older. These characteristics may account for better reproducibility of BP differences between arms in our study. Indeed, Eguchi et al11 reported 2 patients with vascular disease who had large interarm differences that were reproducible. Given that the differences in BP were of prognostic importance, we are led to believe that the differences between arms in our sample were unlikely to be because of random variation.

There are some limitations of our study. Our population was predominantly men, given the make up of the US veterans. Also, there was a high prevalence of vascular disease. Whether these results would hold in people with little vascular disease or who are young is not clear. Although we did not specify that the arm in which the BP is first measured be chosen at random, it is unlikely that the lack of randomization of arms impaired the overall conclusion, because the lack of randomization would only add “noise” to the data.

**Perspectives**

Our data suggest that the right and left arm should not be used interchangeably to obtain BP recordings at repeated visits. Differences between arms are reproducible; therefore, the BP arm should be prespecified. In addition, the simple finding of BP difference between arms confers a higher risk of mortality. Finally, our data show a significant regression to the mean evident within 1 week, which has implications for clinical trials using clinic BP recordings. Thus, a second visit would likely provide more stable estimates of BP, especially in patients with CKD. Larger studies in more diverse populations are needed to confirm the findings of our study.

### Table 3. Partitioning of Variability and Intraclass Correlation Coefficients

<table>
<thead>
<tr>
<th>Random Parameter</th>
<th>Model A</th>
<th>Model B</th>
<th>Model C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between-subject SD</td>
<td>21.3</td>
<td>18.4</td>
<td>18.3</td>
</tr>
<tr>
<td>Between-visit SD</td>
<td>13.7</td>
<td>12.9</td>
<td></td>
</tr>
<tr>
<td>Between-arm SD</td>
<td>12.5</td>
<td>8.4</td>
<td>7.2</td>
</tr>
<tr>
<td>Residual SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−Log likelihood</td>
<td>−17 188.9</td>
<td>−16 115.2</td>
<td>−15 693.0</td>
</tr>
<tr>
<td>Intraclass correlation coefficient</td>
<td>0.74</td>
<td>0.88</td>
<td>0.93</td>
</tr>
</tbody>
</table>

SD is for systolic BP (mm Hg). Progressive model fits are better compared with the nested model (P<0.001).

### Table 4. Hazard of All-Cause Mortality

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hazard Ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model A</td>
</tr>
<tr>
<td>Between-arm difference in systolic BP (10 mm Hg)</td>
<td>1.28 (1.04 to 1.57)</td>
</tr>
<tr>
<td>Systolic BP (10 mm Hg)</td>
<td>1.17 (1.09 to 1.26)</td>
</tr>
<tr>
<td>CKD</td>
<td>3.26 (2.1 to 5.0)</td>
</tr>
<tr>
<td>Age (/y)</td>
<td>1.05 (1.03 to 1.07)</td>
</tr>
<tr>
<td>Log likelihood</td>
<td>−708.0</td>
</tr>
</tbody>
</table>

Progressive model fits are better compared with the nested model (P<0.001).
Disclosures
None.

References
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