Central versus ambulatory blood pressure in the prediction of all-cause and cardiovascular mortalities


Objectives Central systolic (SBP-C) and/or pulse pressure (PP-C) better predicts cardiovascular events than does peripheral blood pressure. The present study compared the prognostic significance of office central blood pressure with multiple measurements of out-of-office ambulatory peripheral blood pressure, with reference to office peripheral systolic (SBP-B) or pulse pressure (PP-B).

Methods In a community-based population of 1014 healthy participants, SBP-C and PP-C were estimated using carotid tonometry, and 24-h systolic (SBP-24 h) and pulse pressure (PP-24 h) were obtained from 24-h ambulatory blood pressure monitoring. Associations of SBP-B, PP-B, SBP-C, PP-C, SBP-24 h, and PP-24 h with all-cause and cardiovascular mortalities over a median follow-up of 15 years were examined by Cox regression analysis.

Results In multivariate analyses accounting for age, sex, BMI, smoking, fasting plasma glucose, and total cholesterol/high-density lipoprotein cholesterol ratio, only PP-C (hazard ratio 1.16, 95% confidence interval 1.01–1.32, per one standard deviation increment) was significantly predictive of all-cause mortality, whereas all but PP-B were significantly predictive of cardiovascular mortality. When SBP-B was simultaneously included in the models, SBP-24 h (2.01, 1.42–2.85) and SBP-C (1.71, 1.21–2.40) remained significantly predictive of cardiovascular mortality. When SBP-C was simultaneously included in the models, SBP-24 h (1.71, 1.16–2.52) remained significantly predictive of cardiovascular mortality.

Conclusion Office central blood pressure is more valuable than office peripheral blood pressure in the prediction of all-cause and cardiovascular mortalities. Out-of-office ambulatory peripheral blood pressure (SBP-24 h) may be superior to central blood pressure in the prediction of cardiovascular mortality, but PP-C may better predict all-cause mortality than SBP-24 h or PP-24 h. J Hypertens 29:454–459 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Keywords: ambulatory blood pressure, central blood pressure, mortality, pulse pressure, target organ damage

Abbreviations: 24h, average 24-h measurements; ABPM, ambulatory blood pressure monitoring; BP, blood pressure; PP-C, central pulse pressure; SBP-C, central systolic blood pressure

0Department of Medicine, Yuan Shan Veterans Hospital, Yilan, 1Department of Medicine, 2Department of Medical Research and Education, Taipei Veterans General Hospital, 3Institute of Biomedical Sciences, Academia Sinica, Taipei, 4Cardiovascular Center, Taichung Veterans General Hospital, Taichung, Taiwan, 5Laboratory of Cardiovascular Science in the National Institute on Aging Intramural Research Program, Baltimore, Maryland, 6Department of Biomedical Engineering, Washington University, St Louis, Missouri, USA, 7Department of Public Health and Cardiovascular Research Center, National Yang-Ming University, Taipei, Taiwan

Correspondence to Chen-Huan Chen, MD, Department of Medical Research and Education, Taipei Veterans General Hospital, No. 201, Sec. 2, Shih-Pai Road, Taipei, Taiwan

Tel: +886 2 28712121x2073; fax: +886 2 28717431; e-mail: chench@vghtpe.gov.tw

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Introduction

Reliability of brachial blood pressure (BP) measurement in the physician’s office is limited by the presence of a random error inherent in casual readings and a systematic error related to the patient’s alerting reaction to the measurement [1,2]. Out-of-office BP measurement, using either home BP monitoring or ambulatory BP monitoring (ABPM) techniques, is devoid of such limitations and is gaining importance in the management of hypertension [1]. In particular, the superiority of averaged 24-h systolic BP (SBP-24 h) obtained from ABPM over office systolic BP in the prediction of cardiovascular events has been confirmed in a large variety of settings [2]. However, a high-quality single visit nurse-recorded brachial systolic BP may be equally as effective as SBP-24 h in predicting target organ damages [3].

The relative roles of central versus peripheral BPs in cardiovascular morbidity and mortality remain unsettled [4]. Brachial BP does not represent BP measured in the central arteries such as the ascending aorta and the carotid arteries [5]. Some studies show that central systolic (SBP-C) and pulse (PP-C) pressure values obtained by noninvasive techniques bear a stronger relationship to target organ damage and cardiovascular mortality than brachial BP [6–8]. In contrast, brachial systolic (SBP-B) and pulse (PP-B) pressures but not SBP-C or PP-C predicted outcome in older female hypertensive patient
[9], and PP-B and PP-C showed similar hazard ratios for the composite clinical end point in the Conduit Artery Function Evaluation study cohort [10]. In addition, measurement of central BP in the physician’s office may also be subject to the alerting reaction. In essence, the relative prognostic value of the office central BP versus the out-of-office ABPM peripheral BP is unknown. Therefore, the objective of this study was to compare SBP-C and PP-C versus SBP-24 h and PP-24 h with reference to SBP-B and PP-B in the prediction of all-cause and cardiovascular mortalities in a community-based study.

Methods
Study population
The present cohort was selected from the previously reported community-based study of 2230 participants (89.2% of the target population of 2500 residents) in Pu-Li and Kinmen, Taiwan [11]. Figure 1 illustrates the generation of the present cohort consisting of 1014 normotensive or untreated hypertensive participants (466 women, 46%), aged 52 ± 13 years with a range of 30–79 years. Characteristics of participants with ABPM who were excluded and included in the present study are shown in the Supplementary Table S1, http://links.lww.com/HJH/A63. Baseline comprehensive cardiovascular evaluation performed in the nonfasting state included complete medical history and physical examination, arterial tonometry and ultrasonography, and echocardiography [12]. The study was approved by the institutional review board of Johns Hopkins University. All study participants gave informed consent.

Blood pressure variables
After being seated for at least 5 min, right arm brachial BP was measured with a mercury sphygmomanometer and a standard-sized cuff (13 cm × 50 cm) by one of four senior cardiologists who had been informed of the standard procedures for BP measurement. SBP-B and brachial diastolic BP values represent the average of at least two consecutive measurements, separated by at least 5 min. PP-B was the difference between SBP-B and brachial diastolic BP.

SBP-C and PP-C were obtained using the carotid tonometry [7]. Right carotid artery pressure waveforms were registered noninvasively by applanation tonometry using a high-fidelity SPC-301 micromanometer (Millar Instrument Inc., Houston, Texas, USA) [12]. Five to 10 consecutive carotid pressure waveforms were ensemble averaged to one waveform. The averaged carotid pressure waveform was then calibrated using brachial mean and diastolic BPs. Brachial mean BP was 1/3 PP-B + brachial diastolic BP. The interobserver and intraobserver variabilities of the estimation of SBP-C and PP-C by carotid tonometry were 0.6 and 0.9% for SBP-C, and 0.6 and 0.3% for PP-C, respectively. The variability values were calculated as the difference between the duplicate values obtained by observers divided by the mean from another 20 participants.

Multiple measurements of the out-of-office brachial BP were obtained from the oscillometric ABPM recorders (Model 90207; SpaceLabs Inc., Redmond, Washington, USA) to calculate SBP-24 h and PP-24 h [11]. Recorders were programmed to measure brachial BP (full inflation, followed by deflation in steps of 8 mmHg) at 20-min intervals during the daytime (from 0700 to 2200 h) and at 60-min intervals during the night-time (from 2200 to 0700 h). The 24-h BP readings were not edited manually, and only participants whose ABPM records contained at least 70% of the total possible readings (64 ± 11) were included in the analysis. The average number of BP recordings obtained was 50 ± 5 during the 24 ± 2 h.

Biochemical variables
Overnight fasting blood samples were acquired for lipids and glucose measurements. Serum cholesterol was measured with a Hitachi autoanalyzer. Serum high-density lipoprotein cholesterol was measured using a precipitation method (Kodak Ektachem HDL Kit). Plasma glucose concentration was determined by a hexokinase/glucose-6-phosphate dehydrogenase method [Glucose (HK) Reagent Kit; Gilford System, Oberlin, Ohio, USA].

Follow-up
The causes and dates of death for those who had deceased within follow-up period after the baseline survey were obtained in all of 1014 participants by linking our database with the National Death Registry through a unique, life-long personal identification number given to every Taiwan citizen. Participants not appearing on the National Death Registry database on 31 December 2007 were considered surviving. The National Death Registry database registers valid information based on the certified death certificates, which were coded according to the
Statistical analysis

The analyses were performed using the statistical package SPSS, version 15.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative variables are expressed as the mean ± standard deviation. Dichotomous variables are presented with percentages. Student’s t-test and $\chi^2$ test were used for between-group comparisons of continuous and dichotomous variables, wherever appropriate. Pearson’s product-moment correlation coefficients between BP variables with age were calculated. To estimate the magnitude of multicollinearity between the BP variables, the variance inflation factor was also calculated [14]. The magnitude of multicollinearity was considered high if the variance inflation factor was more than 5 [14]. Associations of SBP-B, PP-B, SBP-C, PP-C, SBP-24 h, and PP-24 h with all-cause and cardiovascular mortalities over a median follow-up of 15 years were examined by Cox proportional hazard regression analysis, with or without accounting for age, sex, BMI, smoking, fasting plasma glucose, and total cholesterol/high-density lipoprotein cholesterol ratio. SBP-B, SBP-C, or PP-C was also jointly entered into the multivariate Cox regression models. Crude and adjusted hazard ratios and 95% confidence intervals (CIs) were calculated for each standard deviation increment. Two-tailed $P$ value less than 0.05 was considered statistically significant.

Results

Baseline characteristics

The baseline characteristics of the participants who were alive ($n = 813$) at the end of the follow-up and who had died from any ($n = 201$) or cardiovascular ($n = 55$) causes are shown in Table 1. The causes for cardiovascular deaths included cardiac diseases ($n = 21$) and either ischemic or hemorrhagic stroke ($n = 34$). In general, survivors were significantly younger, smoked less, and had lower total cholesterol/high-density lipoprotein cholesterol ratio, lower peripheral, central, and ABPM BPs, than participants who had died from any or cardiovascular causes.

Correlations among blood pressure variables and age

Correlation coefficients between age and BP variables and between BP variables are provided in Table 2. Among the six central and peripheral BP variables, PP-C had the highest correlation with age, followed by PP-24 h, PP-B, SBP-C, SBP-B, and SBP-24 h. The correlation between ambulatory BP and office central BP appeared to be stronger than that between ambulatory BP and office brachial BP.

Associations of blood pressure variables with mortality

In univariate analysis, all six BP variables significantly predicted all-cause and cardiovascular mortalities (Table 3). However, only PP-C (hazard ratio 1.16, 95% CI 1.01–1.32) was significantly predictive of all-cause mortality (Fig. 2a), and all but PP-B were significantly predictive of cardiovascular mortality (Fig. 2b), after adjustment for age, current smoking, fasting plasma glucose, and ratio of total cholesterol to high-density lipoprotein cholesterol. SBP-24 h had the highest hazard ratio (1.97, 95% CI 1.49–2.60), followed by SBP-C (1.72, 95% CI 1.32–2.23).

When SBP-B was simultaneously included in the multivariate models, PP-C was no longer significantly predictive of all-cause mortality, whereas SBP-24 h and SBP-C but not PP-24 h or PP-C remained significantly predictive of cardiovascular mortality (Table 4).

When SBP-C was simultaneously included in the multivariate models, only SBP-24 h remained significantly predictive of cardiovascular mortality (Table 4).

When PP-C was simultaneously included in the multivariate models, both SBP-24 h and SBP-C remained significantly predictive of cardiovascular mortality (Table 4).

Table 1 Baseline characteristics of the study population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survival ($n = 813$)</th>
<th>All-cause mortality ($n = 201$)</th>
<th>$P$ values*</th>
<th>CV mortality ($n = 55$)</th>
<th>$P$ values*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49 ± 11</td>
<td>64 ± 11</td>
<td>&lt;0.001</td>
<td>64 ± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>433 (53)</td>
<td>115 (57)</td>
<td>0.314</td>
<td>29 (53)</td>
<td>0.699</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>188 (23)</td>
<td>66 (33)</td>
<td>0.004</td>
<td>19 (35)</td>
<td>0.054</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>25 ± 4</td>
<td>24 ± 4</td>
<td>0.122</td>
<td>25 ± 3</td>
<td>0.995</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/l)</td>
<td>5.5 ± 1.1</td>
<td>5.8 ± 1.8</td>
<td>0.073</td>
<td>6.0 ± 2.6</td>
<td>0.239</td>
</tr>
<tr>
<td>Total cholesterol/HDL</td>
<td>4.1 ± 1.2</td>
<td>4.3 ± 1.3</td>
<td>0.014</td>
<td>4.5 ± 1.2</td>
<td>0.008</td>
</tr>
<tr>
<td>SBP-24 h (mmHg)</td>
<td>126 ± 17</td>
<td>132 ± 18</td>
<td>&lt;0.001</td>
<td>141 ± 18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PP-24 h (mmHg)</td>
<td>45 ± 8</td>
<td>50 ± 11</td>
<td>&lt;0.001</td>
<td>53 ± 13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP-C (mmHg)</td>
<td>125 ± 23</td>
<td>135 ± 26</td>
<td>&lt;0.001</td>
<td>146 ± 25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PP-C (mmHg)</td>
<td>39 ± 14</td>
<td>50 ± 19</td>
<td>&lt;0.001</td>
<td>55 ± 22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP-B (mmHg)</td>
<td>138 ± 20</td>
<td>145 ± 24</td>
<td>&lt;0.001</td>
<td>152 ± 21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PP-B (mmHg)</td>
<td>49 ± 16</td>
<td>57 ± 18</td>
<td>&lt;0.001</td>
<td>61 ± 18</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

24-h, average 24-h measurements; B, brachial measurements; C, central measurements; CV, cardiovascular; HDL, high-density lipoprotein cholesterol; PP, pulse pressure.

* $P$ values of all-cause mortality versus survival.

$P$ values of cardiovascular death versus survival.
Discussion
In this homogeneous Taiwanese population without previous history of diabetes or any documented significant cardiovascular disease, we found that all office central and peripheral and out-of-office ambulatory peripheral BP variables were significantly related to 15-year all-cause and cardiovascular mortalities. Among the six central and peripheral BP variables, only PP-C was significantly predictive of all-cause mortality after adjustment for other cardiovascular risk factors. On the other hand, SBP-24 h, PP-24 h, SBP-C, PP-C, and SBP-B predicted cardiovascular mortality independently of other cardiovascular risk factors. In addition, both SBP-24 h and SBP-C were significantly predictive of cardiovascular mortality independently of SBP-B or PP-C. Moreover, SBP-24 h remained predictive of cardiovascular mortality independently of SBP-C and other cardiovascular risk factors. Therefore, both office central and out-of-office ambulatory peripheral BP provided prognostic values superior to the conventional office peripheral BP. The results are relevant to the differential roles of central versus peripheral and systolic versus PPs in the pathogenesis of cardiovascular outcomes and may support the measuring of office central BP in the management of hypertension.

It has been recognized that PP exerts direct cyclic stress on conduit vessels and target organs such as carotid arteries and kidneys, and systolic BP mediates left ventricular hypertrophy through increased end-systolic stress [15,16]. In addition, PP-C clearly better predicts incident cardiovascular disease events than PP-B [17]. Our previous study reconfirmed the ascendancy of SBP-C/ SBP-B over PP-C/PP-B in determining left ventricular mass, whereas PP-C is more important than SBP-C or PP-B in determining carotid intima–media thickness [7]. The present study further extended that PP-C may be more important than PP-B, PP-24 h, SBP-C, and SBP-24 h in the prediction of all-cause mortality in the general population.

The superiority of PP-C over PP-B for predicting all-cause mortality has only been shown in patients with end-stage renal disease [4,18]. In the present study, PP-C exhibited the best correlation with age among all BP variables and was the only BP measurement that was significantly associated with all-cause mortality after adjustment for other cardiovascular risk factors. These results may support that PP-C is a more direct indicator of central artery stiffness and a better marker of vascular aging than other BP variables. Although SBP-24 h and PP-24 h were out-of-office measurements devoid of the random and systemic errors [1,2], they were still peripheral BPs and not sufficiently representative of the large artery stiffness. It has been shown that a single visit carotid-femoral pulse wave velocity but not PP-24 h predicted a composite of cardiovascular outcomes above

Table 2 Relationship among blood pressure variables and age

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age</th>
<th>SBP-B</th>
<th>PP-B</th>
<th>SBP-C</th>
<th>PP-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP-24 h</td>
<td>0.240</td>
<td>0.678</td>
<td>1.85</td>
<td>0.457</td>
<td>1.26</td>
</tr>
<tr>
<td>PP-24 h</td>
<td>0.410</td>
<td>0.553</td>
<td>1.44</td>
<td>0.571</td>
<td>1.48</td>
</tr>
<tr>
<td>SBP-C</td>
<td>0.306</td>
<td>0.722</td>
<td>2.09</td>
<td>0.526</td>
<td>1.38</td>
</tr>
<tr>
<td>PP-C</td>
<td>0.486</td>
<td>0.570</td>
<td>1.48</td>
<td>0.597</td>
<td>1.55</td>
</tr>
<tr>
<td>SBP-B</td>
<td>0.245</td>
<td>–</td>
<td>2.58</td>
<td>0.782</td>
<td>2.09</td>
</tr>
<tr>
<td>PP-B</td>
<td>0.354</td>
<td>0.782</td>
<td>2.57</td>
<td>–</td>
<td>1.38</td>
</tr>
</tbody>
</table>

24-h, average 24-h measurements; B, brachial measurements; C, central measurements; PP, pulse pressure. Values in the parentheses are the variance inflation factors. The magnitude of multicollinearity was considered high if the variance inflation factor was >5. *P value <0.001.

Table 3 Hazard ratios and 95% confidence intervals per one-standard deviation increment of each variable for all-cause and cardiovascular mortalities by univariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>All-cause mortality</th>
<th>Cardiovascular mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP-24 h (17 mmHg)</td>
<td>1.37, 1.20–1.56</td>
<td>2.08, 1.65–2.62</td>
</tr>
<tr>
<td>SBP-C (24 mmHg)</td>
<td>1.42, 1.25–1.61</td>
<td>2.05, 1.60–2.58</td>
</tr>
<tr>
<td>SBP-B (23 mmHg)</td>
<td>1.33, 1.16–1.52</td>
<td>1.70, 1.30–2.16</td>
</tr>
<tr>
<td>PP-24 h (9 mmHg)</td>
<td>1.64, 1.46–1.85</td>
<td>2.06, 1.67–2.54</td>
</tr>
<tr>
<td>PP-C (16 mmHg)</td>
<td>1.62, 1.49–1.85</td>
<td>1.98, 1.63–2.41</td>
</tr>
<tr>
<td>PP-B (17 mmHg)</td>
<td>1.42, 1.27–1.59</td>
<td>1.62, 1.34–1.95</td>
</tr>
</tbody>
</table>

Parentheses indicate standard deviations. 24-h, average 24-h measurements; B, brachial measurements; C, central measurements; PP, pulse pressure.
and beyond traditional cardiovascular risk factors, including 24-h mean BP [19]. Therefore, it is possible that an office measurement of large artery stiffness by PP-C or carotid-femoral pulse wave velocity is more important than out-of-office measurements of peripheral BP in the prediction of all-cause and cardiovascular mortalities.

We have previously shown that SBP-C was superior to PP-C in predicting cardiovascular mortality, probably because of the stronger correlation of SBP-C with left ventricular mass than PP-C [7]. In contrast, other studies suggest that PP-C may be associated more with cardiovascular disease events than SBP-C [4,6]. The differential importance of SBP-C versus PP-C in predicting cardiovascular outcomes is likely related to the ethnic differences in cardiovascular disease risk and presentation [20]. In this study population, the correlation coefficients with left ventricular mass for SBP-B, SBP-C, and SBP-24 were 0.379, 0.434, and 0.460, respectively (supplementary Table S2, http://links.lww.com/HJH/A63). Therefore, the finding that SBP-24 h was better than SBP-C and PP-C in the prediction of cardiovascular mortality was probably due to the stronger association of SBP-24 h with left ventricular mass than SBP-C and PP-C. Left ventricular mass reflects and integrates the long-term cumulative effect of several hemodynamic and nonhemodynamic risk factors for cardiovascular disease and may be a useful marker for the severity of hypertension in a population [15]. The results are consistent with the predominant role of hypertension in causing cardiovascular mortality in this Chinese population [21].

Limitations of the present study

Nonfatal events were not available and the rate for cardiovascular mortality was low in this relative low-risk study population. Other follow-up data, including the use of medications and development of nonfatal cardiovascular events were not available. Therefore, the potential impact of medications during the follow-up period on the prediction of mortalities with the baseline central and ambulatory BP values could not be adjusted. BP may fall after meals, especially in the elderly [22]. In the present study, central BP was measured in the morning or afternoon and might have been variously influenced by food intake. In contrast, ABPM had the advantage of regularly measuring BP for 24 h in all participants and, therefore, minimized the confounding effect of food intake on the associations between BP and cardiovascular mortality. Peripheral SBP-24 h during ABPM might simply be better than the office SBP-C because of regression to the mean, that is, more precise measurements. Therefore, a comparison of central and peripheral BP during ABPM is required in the future studies.

The present study estimated central BP using arterial tonometry derived carotid pressure waveforms calibrated by the brachial diastolic and mean BPs [23]. Therefore, the errors from the measurement of brachial BP by the mercury sphygmomanometer may transmit to the estimated carotid BP [23]. In addition, a small pressure difference (around 2 mmHg) may exist between the carotid and aortic systolic BP because of the amplification phenomenon [23].

The presence of multicollinearity might be responsible for the insignificance of PP-C in the prediction of cardiovascular mortality when SBP-B or SBP-C was simultaneously included in the multivariate analyses. However, the ‘negative results’ were considered reasonable because the magnitude of multicollinearity was low (all variance inflation factors <5) and all PP variables consistently showed smaller hazard ratios for cardiovascular mortality than their corresponding systolic BP variables in the multivariate prediction models without the inclusion of another BP variable (Fig. 2b).

In conclusion, office central BP is more valuable than office peripheral BP in the prediction of all-cause and cardiovascular mortalities. Out-of-office ambulatory peripheral BP (SBP-24 h) may be superior to central BP in the prediction of cardiovascular mortality, but PP-C may better predict all-cause mortality than SBP-24 h or PP-24 h.

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There are no conflicts of interest.

References


