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CENTRAL VERSUS AMBULATORY BLOOD PRESSURE IN THE PREDICTION OF ALL-CAUSE AND CARDIOVASCULAR MORTALITIES

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Abstract

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-hour systolic (SBP-24h) and pulse pressure (PP-24h) were obtained from 24-hour ambulatory blood pressure monitoring. Associations of SBP-B, PP-B, SBP-C, PP-C, SBP-24h, and PP-24 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, body mass index, smoking, fasting plasma glucose, and total cholesterol/high-density lipoprotein cholesterol, only PP-C [hazard ratio 1.16, 95% confidence interval 1.01–1.32, per 1 standard deviation increment] was significantly

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predictive of all-cause mortality, while all but PP-B were significantly predictive of cardiovascular mortality. When SBP-B was simultaneously included in the models, SBP-24h [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-24h [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-24h) may be superior to central blood pressure in the prediction of cardiovascular mortality, but PP-C may better predict all-cause mortality than SBP-24h or PP-24h.

Keywords

Ambulatory blood pressure; Central blood pressure; Pulse pressure; Target organ damage; Mortality

Introduction

Reliability of brachial blood pressure (BP) measurement in the physician's office is limited by the presence of a random error inherent to 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-hour systolic BP (SBP-24h) 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-24h in predicting target organ damages.[3]

The relative roles of central versus peripheral blood pressures 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 hazards 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-24h and PP-24h 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 subjects with ABPM who were excluded and included in the present study are shown in the Supplementary Table S1. Baseline comprehensive cardiovascular evaluation performed in the non-fasting 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 subjects gave informed consent.

Blood pressure variables

After being seated for at least 5 minutes 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 minutes. 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 ten 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 $1/3 \text{ PP-B} + \text{brachial diastolic BP}$. The inter- and intra-observer 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 subjects.

Multiple measurements of the out-of-office brachial BP were obtained from the oscillometric ABPM recorders (Model 90207, SpaceLabs Inc., Redmond, Washington) to calculate SBP-24h and PP-24h.[11] Recorders were programmed to measure brachial BP (full inflation, followed by deflation in steps of 8 mmHg) at 20-minute intervals during the daytime (from 7 A.M. to 10 P.M.) and at 60-minute intervals during the nighttime (from 10 P.M. to 7 A.M.). The 24-hour BP readings were not edited manually, and only subjects whose ABPM records contained $\geq 70\%$ 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 hours.

Biochemical variables

Overnight fasting blood samples were acquired for lipids and glucose measurements. Serum cholesterol was measured with a Hitachi auto-analyzer. 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, OH].

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. Subjects not appearing on the National Death Registry database on December 31, 2007 were considered surviving. The National Death Registry database registers valid information based on the certified death certificates, which were coded according to the International Classification of Disease, Ninth Revision (ICD-9). The ICD-9 codes representing cardiovascular deaths were 390–459. The accuracy of cause-of-death coding in Taiwan's National Death Registry database has been validated. [13]

Statistical Analysis

The analyses were performed using the statistical package SPSS, version 15.0 (SPSS Inc.). Quantitative variables are expressed as the mean $\pm$ standard deviation. Dichotomous variables are presented with percents. Student's *t* test and Chi-square test were used for between-group comparisons of continuous and dichotomous variables where appropriate. Pearson's product-moment correlation coefficients between BP variables with age were calculated. To estimate the magnitude of multi-collinearity between the BP variables, the variance inflation factor was also calculated.[14] The magnitude of multi-collinearity was considered high if the variance inflation factor was >5 . [14] Associations of SBP-B, PP-B, SBP-C, PP-C, SBP-24h, and PP-24 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, body mass index, 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 multi-variate Cox regression models. Crude and adjusted hazard ratios and 95% confidence intervals were calculated for each standard deviation increment. Two-tailed $P < 0.05$ was considered statistically significant. Statistical analyses were performed using the statistical package SPSS 15.0 (SPSS Inc).

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 BP variables and Age

Correlation coefficients between age and BP variables and between BP variables are provided in Table 2. Among the 6 central and peripheral BP variables, PP-C had the highest correlation with age, followed by PP-24h, PP-B, SBP-C, SBP-B, and SBP-24h. The correlation between ambulatory BP and office central BP appeared to be stronger than that between ambulatory BP and office brachial BP.

Associations of BP variables with mortality

In univariate analysis, all 6 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 (Figure 2A), and all but PP-B were significantly predictive of cardiovascular mortality (Figure 2B), after adjustment for age, current smoking, fasting plasma glucose, and ratio of total cholesterol to high-density lipoprotein cholesterol. SBP-24h 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, while SBP-24h and SBP-C but not PP-24h or PP-C remained significantly predictive of cardiovascular mortality (Table 4).

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

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

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 6 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-24h, PP-24h, SBP-C, PP-C, and SBP-B predicted cardiovascular mortality independently of other cardiovascular risk factors. In addition, both SBP-24h and SBP-C were significantly predictive of cardiovascular mortality independently of SBP-B or PP-C. Moreover, SBP-24h 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 pulse pressures 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 pulse pressure 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-24h, SBP-C, and SBP-24h 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-24h and PP-24h 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-24h predicted a composite of cardiovascular outcomes above 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). Therefore, the finding that SBP-24h was better than SBP-C and PP-C in the prediction of cardiovascular mortality was probably due to the stronger association of SBP-24h 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 non-hemodynamic 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

Non-fatal 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 non-fatal 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 hours in all participants and therefore minimized the confounding effect of food intake on the associations between BP and cardiovascular mortality. Peripheral SBP-24 during ABPM might simply be better than the office SBP-C because of regression to the mean – i.e., more precise measurements. Therefore, a comparison of central and peripheral BP during ABPM is required in the future studies.

The present study estimated carotid 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 multi-collinearity 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 multi-variate analyses. However, the “negative results” were considered reasonable because the magnitude of multi-collinearity was low (all variance inflation factors <5) and all pulse pressure 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 (Figure 2B).

In 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-24h) may be superior to central blood pressure in the prediction of cardiovascular mortality, but PP-C may better predict all-cause mortality than SBP-24h or PP-24h.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Selection of study population. ABPM = ambulatory blood pressure monitoring.

Figure 2.

Hazards ratios and 95% confidence intervals of the individual blood pressure variables per one-SD increment for all-cause mortality (A) and cardiovascular mortality (B), accounting for age, sex, body mass index, smoking, fasting plasma glucose, and total cholesterol/high-density lipoprotein cholesterol. 24-h = average 24-hour measurements; B = brachial measurements; C = central measurements; D = average daytime measurements; N = average nighttime measurements. PP = pulse pressure; SBP = systolic blood pressure.

Table 1

Baseline characteristics of the study population

Variable	Survival (n= 813)	All-cause mortality (n= 201)	P values [*]	CV mortality (n= 55)	P values [†]
Age, years	49 ± 11	64 ± 11	<0.001	64 ± 11	<0.001
Male gender, n (%)	433 (53)	115 (57)	0.314	29 (53)	0.939
Current smoking, n (%)	188 (23)	66 (33)	0.004	19 (35)	0.054
Body mass index, kg/m ²	25 ± 4	24 ± 4	0.122	25 ± 3	0.995
Fasting plasma glucose, mmol/l	5.5 ± 1.1	5.8 ± 1.8	0.073	6.0 ± 2.6	0.239
Total cholesterol/HDL	4.1 ± 1.2	4.3 ± 1.3	0.014	4.5 ± 1.2	0.008
SBP-24h, mmHg	126 ± 17	132 ± 18	<0.001	141 ± 18	<0.001
PP-24h, mmHg	45 ± 8	50 ± 11	<0.001	53 ± 13	<0.001
SBP-C, mmHg	125 ± 23	135 ± 26	<0.001	146 ± 25	<0.001
PP-C, mmHg	39 ± 14	50 ± 19	<0.001	55 ± 22	<0.001
SBP-B, mmHg	138 ± 23	145 ± 24	<0.001	152 ± 21	<0.001
PP-B, mmHg	49 ± 16	57 ± 18	<0.001	61 ± 18	<0.001

^{*} : P values of all-cause mortality vs. survival;

[†] : P values of CV death vs. survival.

24-h = average 24-hour measurements; B = peripheral measurements; C = central measurements; CV = cardiovascular; HDL = high-density lipoprotein cholesterol; PP = pulse pressure; SBP = systolic blood pressure.

Table 2

Relationship among blood pressure variables and age

Variable	Age	SBP-B	PP-B	SBP-C	PP-C
SBP-24h	0.240 [‡]	0.678 [‡] (1.85)	0.457 [‡] (1.26)	0.809 [‡] (2.89)	0.588 [‡] (1.53)
PP-24h	0.410 [‡]	0.553 [‡] (1.44)	0.571 [‡] (1.48)	0.671 [‡] (1.82)	0.735 [‡] (2.17)
SBP-C	0.307 [‡]	0.722 [‡] (2.09)	0.526 [‡] (1.38)	-	0.817 [‡] (3.01)
PP-C	0.486 [‡]	0.570 [‡] (1.48)	0.597 [‡] (1.55)	0.817 [‡] (3.01)	-
SBP-B	0.245 [‡]	-	0.782 [‡] (2.58)	0.722 [‡] (2.09)	0.570 [‡] (1.48)
PP-B	0.354 [‡]	0.782 [‡] (2.57)	-	0.526 [‡] (1.38)	0.597 [‡] (1.55)

[‡]; P value <0.01;

[‡]; P value <0.001.

Parentheses are the variance inflation factors. The magnitude of multi-collinearity was considered high if the variance inflation factor was >5.

24-h = average 24-hour measurements; B = peripheral measurements; C = central measurements; PP = pulse pressure; SBP = systolic blood

Table 3

Hazard ratios and 95% confidence intervals per 1-standard deviation increment of each variable for all-cause and cardiovascular mortalities by univariate analysis

Variable	All-cause mortality	Cardiovascular mortality
SBP-24h (17 mmHg)	1.37, 1.20–1.56	2.08, 1.65–2.62
SBP-C (24 mmHg)	1.42, 1.25–1.61	2.05, 1.63–2.58
SBP-B (23 mmHg)	1.33, 1.16–1.52	1.70, 1.33–2.16
PP-24h (9 mmHg)	1.64, 1.46–1.85	2.06, 1.67–2.54
PP-C (16 mmHg)	1.66, 1.49–1.85	1.98, 1.63–2.41
PP-B (17 mmHg)	1.42, 1.27–1.59	1.62, 1.34–1.95

Parentheses indicate standard deviations.

24-h = average 24-hour measurements; B = peripheral measurements; C = central measurements; PP = pulse pressure; SBP = systolic blood pressure.

Table 4

Hazard ratios and 95% confidence intervals per 1-standard deviation increment of each variable for all-cause and cardiovascular mortalities by multivariate analysis

Variables	All-cause mortality	Cardiovascular mortality
Adjust for SBP-B and other cardiovascular risk factors		
SBP-24h (17 mmHg)	1.14, 0.93–1.39	2.01, 1.42–2.85
PP-24h (9 mmHg)	1.11, 0.94–1.32	1.35, 0.99–1.83
SBP-C (24 mmHg)	1.11, 0.91–1.34	1.71, 1.21–2.40
PP-C (16 mmHg)	1.15, 0.98–1.34	1.30, 0.98–1.72
Adjust for SBP-C and other cardiovascular risk factors		
SBP-24h (17 mmHg)	1.12, 0.90–1.39	1.71, 1.16–2.52
PP-24h (9 mmHg)	1.09, 0.91–1.31	1.12, 0.81–1.56
PP-C (16 mmHg)	1.20, 0.93–1.56	0.76, 0.48–1.22
Adjust for PP-C and other cardiovascular risk factors		
SBP-24h (17 mmHg)	1.08, 0.90–1.30	1.90, 1.37–2.63
PP-24h (9 mmHg)	1.04, 0.86–1.27	1.30, 0.91–1.85
SBP-C (24 mmHg)	0.95, 0.72–1.27	2.21, 1.33–3.66

Parentheses indicate standard deviations.

Other cardiovascular risk factors include age, sex, body mass index, smoking, fasting plasma glucose, and total cholesterol/high-density lipoprotein cholesterol.

24-h = average 24-hour measurements; B = brachial measurements; C = central measurements; N = average nighttime measurements. PP = pulse pressure; SBP = systolic blood pressure.