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# Comparison of Clinic and Ambulatory Blood Pressure in Response to Antihypertensive Drugs in Chinese Patients

XIAO-RU CHENG, YANG WANG, BO HU, XUAN JIA, AND WEI LI[1]

*National Center for Cardiovascular Diseases, Cardiovascular Institute & Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100037, China*

**Objective** To compare the difference between 24-h ambulatory blood pressure (ABP) and trough clinic blood pressure (CBP) after 8 weeks of therapy. **Methods** The study used meta-regression analysis to summarize three randomized, double-blind, active controlled trials in order to compare the difference between the magnitude of the reduction in 24-h average ABP and CBP Patients. Chinese patients with seated diastolic blood pressure (SDBP) 95-115 mmHg and ambulatory diastolic blood pressure (ADBP) $\geqslant$85 mmHg. **Results** The average age of 126 patients was 47.7 ± 8.3 years, ranging from 25 to 67 (95 males and 31 females). All regimens reduced 24-h ABP and CBP after 8 weeks of treatment. In the 126 patients the baseline 24-h SBP and DBP values (142.7/94.4 mmHg) were markedly lower than those for clinic values (152.6/102.6 mmHg; $P$<0.0001). Similarly, the 24-h SBP and DBP values (132.7/87.7 mmHg) in week 8 were markedly lower than the clinic values (138.9/92.7 mmHg; $P$<0.0001). The differences between the treatment-induced reductions in 24-h ABP and CBP were statistically significant (the difference was 3.7/3.3 mmHg for SBP/DBP, $P$=0.0069/$P$<0.0001). **Conclusion** All regimens significantly reduced seated CBP and ABP. The effect of antihypertensive treatment was greater on CBP than that on ABP, suggesting that assessment on effectiveness of an antihypertensive treatment using CBP readings only has to be carefully interpreted, and a more systematic application of ABP monitoring should be adopted.

**Key words**: Ambulatory blood pressure; Antihypertensive treatment; Clinic blood pressure; Essential Hypertension

## INTRODUCTION

Hypertension, an important public health problem in both developing and developed countries, is associated with an increased risk of cardiovascular diseases[1-2]. The prevalence of hypertension among the Chinese elderly who have systolic blood pressure (SBP) above 140 mmHg or diastolic blood pressure (DBP) above 90 mmHg is particularly high[3]. Surveillances are therefore deemed necessary to evaluate the development and control of hypertension in the community.

Monitoring trough clinic blood pressure (CBP) is a simple and useful methods of assessing the efficacy of an antihypertensive agent[4], but it is not accurate enough to assess the appropriateness of dosing. An isolated resting measurement does not estimate the variability of blood pressure that occurs throughout the day and night[5]. Ambulatory blood pressure measurement (ABPM) is very useful to evaluate the prognosis data replacing conventionally acquired data; as the latter have been validated of their prognostic significance. ABPM remains a gold standard for determining the minimal active dose of an antihypertensive drug[2] and can demonstrate the duration of effect of antihypertensive agents. In this regard, 24-h ABPM monitors patients' blood pressures continuously in their usual environments, and provides a more realistic profile of blood pressure change associated with administration of an antihypertensive drug[5-6]. In addition, ABPM is known to minimize placebo effect[7]. The use of ABPM in addition to CBP in patients with borderline hypertension greatly increases the possibility of identifying those individuals who are at a very small risk of developing future hypertension. This could potentially lead to considering savings in patient anxiety, physician time, and resource consumption[8].

The present study examined the relationship between CBP and ABP in 126 Chinese patients who were randomized in three clinical trials and administered with different antihypertensive drugs

[1]Correspondence should be addressed to Prof. Wei LI. Tel: 86-10-88398106. Fax: 86-10-88398106.

Biographical note of the first author: Xiao-Ru CHENG, female, born in 1975, research assistant at the National Center for Cardiovascular Diseases, Cardiovascular Institute & Fuwai Hospital, majoring in occupational and environmental health. E-mail: chengxr99@sohu.com

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for a period of 8 weeks.

## METHODS AND SUBJECTS

### *Selection of Patients*

Total 126 patients (men=95; women=31) were recruited. After patients had signed a consent form approved by the IEC (Institutional Ethical Committee), a medical history of each patient was obtained and a physical examination and laboratory tests were performed. Patients had newly discovered or established mild-to-moderate essential hypertension with seated diastolic blood pressure (SDBP) being 95-115 mmHg and also had a mean 24 h ambulatory diastolic blood pressure (ADBP) ⩾85 mmHg at baseline were included in the study. Patients were excluded from the study if they had specific concomitant diseases that would present safety hazards, or were being administered concomitant medications likely to interfere with the assessment of safety or efficacy (e.g. drugs potentially affecting blood pressure).

### *Study Design*

The study used meta-regression analysis to summarize three randomized, double-blind, active controlled trials. These were fixed-dose trials involving similar mild to moderate hypertensive patients. The SpaceLabs 90207 ABPM devices were used, and each trial comprised a 2-week placebo period and an 8-week treatment period. For the 8-week, double-blind, parallel-group period, patients were randomly assigned to one of the following treatments: 50 mg losartan, 50 mg losartan + 12.5 mg hydrochlorothiazide (HCTZ); 8 mg candeshatan, 10 mg enalapril once a day; 100 mg bevantolol or 100 mg metoprolol twice a day. Treatment doses were doubled at week 4 if clinic DBP was ⩾90 mmHg except for metoprolol, which was increased to 150 mg twice a day if clinic DBP was ⩾90 mmHg at week 4. When medication was used once a day, the patients were instructed to take it between 08:00 and 10:00. While in case twice a day, the patients were asked to take their first medication in morning between 08:00 and 10:00 followed by the second one approximately 12 h later. All drugs administered during the placebo lead-in and double-blind periods were identical in appearance and taste. During the double-blinding therapy, patients returned for clinic visits during week 2, 4, 6, and 8.

### *ABPM Monitoring*

ABPM was performed using a calibrated portable device (model 90207; SpaceLabs, USA) at the end of the placebo lead-in period (baseline) and on the day prior to or on the day of week 8 visit. Recordings were initiated between 08:00 and 10:00 on weekdays. Prior to each recording, accuracy of the device was confirmed by sphygmomanometry (using a T tube) and auscultation. Readings were taken every 20 min from 06:00 to 22:00 and every 30 min from 22:00 to 06:00. Subjects were subjected to ABPM under the baseline conditions when they were free of medication, prior to and after 8 weeks of therapy. Participants were instructed to continue their usual activities with minimal restrictions, but to follow a similar schedule during the test of ABPM. Patients were required to wear the device for a minimum of 26 h after the proceeding day's time of its application. At least 80% of the required recordings had to be available for inclusion in the analysis. Means of ambulatory measurements were assessed by the time interval between consecutive readings. Day and night were defined using short fixed clock time periods, ranging from 6:00 to 22:00 and from 22:00 to 6:00.

### *Selection of ABPM Data*

The data were selected using the following quality control guidelines: 24-h recording, elimination of aberrant values (such as DBP⩾SBP, DBP <40 mmHg or >140 mmHg, SBP <50 mmHg or >240 mmHg) except if clinically justified, elimination of recordings containing <80% of validated measurements, absence of > 2 h averaging interval.

### *CBP Measurements*

During all clinic visits, CBP were measured using a calibrated mercury sphygmomanometer. The tested drug was withheld on mornings of clinic visits until after the CBP had been recorded. After a patient had seated restfully for at least 5-10 min, blood pressure was determined by calculating the mean of three replicated measurements taken 1 min apart.

### *Statistical Methods*

The mean 24 h ABP was defined as an average of the hourly mean ABP values for 24 h after the morning dosing. The primary outcome measure (i.e. change of 24 h mean ABP from baseline to week 8) was calculated for those patients whose ABP data were sufficient to compute a 24 h average ABP at baseline and after 8 weeks. The CBP analyses included the data for all patients who had a baseline CBP and at least one during-therapy CBP evaluation. The heterogeneity for the effects of treatment on CBP and 24-h ABP were compared through meta-regression analysis of the data provided by the

three trials, weighted by their size.

Quantitative variables were recorded using descriptive statistics (number of patients, mean, standard deviation) and qualitative variables by observed and relative frequencies. The correlation coefficients were computed by Pearson correlation. The possible effects of different baseline values on the drug-induced changes in CBP and ABP were assessed by multiple regression analysis and by analysis of covariance, taking baseline blood pressure values as a covariate. All tests were two-sided, and the limit of statistical significance was set at $P<0.05$. All of the statistical analysis were performed with SAS® software (SAS Institute Inc. *SAS/STAT® Software*, Release 9.1).

## RESULTS

### *Demographic and Baseline Characteristics*

The average age of 126 patients was 47.7 ± 8.3 years, ranging from 25 to 67. Among them, 75% were men. Table 1 summarizes the characteristics of the patients at baseline.

TABLE 1

Demographic and Baseline Characteristics

| Characteristic | 50 mg Losartan | 50 mg Losartan/ 12.5 mg HCTZ | 8 mg Candeshatan | 10 mg Enalapril | 100 mg Bevantolol | 100 mg Metoprolol |
|---|---|---|---|---|---|---|
| | Once a Day | Once a Day | Once a Day | Once a Day | Twice a Day | Twice a Day |
| | (*n*=20) | (*n*=19) | (*n*=19) | (*n*=16) | (*n*=24) | (*n*=28) |
| Sex (*n*, %) | | | | | | |
| Male | 14 (70.0) | 14 (73.7) | 15 (78.9) | 12 (75.0) | 19 (79.2) | 21 (75.0) |
| Age (yrs, $\bar{x} \pm s$ ) | | | | | | |
| | 47.0±10.3 | 49.2±11.7 | 50.6±6.7 | 52.3±4.2 | 45.7±6.6 | 44.3±6.5 |
| BMI (Kg/m$^2$, $\bar{x} \pm s$ ) | | | | | | |
| | 26.6±2.3 | 26.0±2.8 | 26.8±2.0 | 27.3±1.6 | 26.7±3.2 | 26.4±3.4 |
| Mean 24 h ABP (mmHg, $\bar{x} \pm s$ ) | | | | | | |
| Diastolic | 94.2±4.7 | 92.8±6.0 | 92.7±7.4 | 94.1±7.6 | 96.3±6.8 | 95.3±8.5 |
| Systolic | 142.0±13.5 | 138.4±10.6 | 143.8±14.7 | 142.9±11.1 | 133.1±12.3 | 143.3±13.9 |
| Mean CBP (mmHg, $\bar{x} \pm s$ ) | | | | | | |
| Diastolic | 104.2±6.0 | 101.8±6.1 | 101.3±5.5 | 100.2±5.2 | 104.1±5.3 | 102.8±7.4 |
| Systolic | 150.1±15.9 | 146.7±11.7 | 154.6±11.7 | 152.3±14.5 | 152.4±11.5 | 157.4±17.0 |

### *Meta-analysis*

Table 2 shows the results of the meta-regression carried out on 3 trials. The results showed that the 3 trials were consistent (all $P<0.05$).

TABLE 2

Meta-regression Results Among the Three Trials

| | Test for Heterogeneity | |
|---|---|---|
| | *Chi-square* | *P* |
| Reduction in 24-h SBP | 1.32 | 0.52 |
| Reduction in 24-h DBP | 1.17 | 0.41 |
| Reduction in Clinic SBP | 0.65 | 0.72 |
| Reduction in Clinic DBP | 1.16 | 0.56 |

### *Relationships Between CBP and ABP*

The baseline 24-h SBP and DBP values (142.7/94.4 mmHg) were markedly lower than that for clinic SBP and DBP values (152.6/102.6 mmHg; $P<0.0001$). Similarly, the 24-h SBP and DBP values in week 8 (132.7/87.7 mmHg) were markedly lower than those for clinic SBP and DBP (138.9/92.7 mmHg; $P<0.0001$). The baseline CBP and 24-h ABP values were significantly related to each other (SBP/DBP: $r=0.64/0.67$, both $P<0.0001$) and so were that in week 8 (SBP/DBP: $r= 0.65/0.65$; both $P<0.0001$).

The differences between the treatment-induced reductions in 24-h ABP and CBP were statistically significant (the difference was 3.7/3.3 mmHg for SBP/DBP, $P=0.0069/P<0.0001$). In addition, the correlation between changes in 24-h ABP and CBP were significant ($r=0.45$ and 0.50 for SBP and DBP, respectively; $P<0.01$ for both).

Table 3 shows the results of multiple regression analysis. The treatment-induced reductions in 24-h SBP were significantly related, not only to the reductions in the corresponding clinic values, but also to the clinic and 24-h SBP values recorded at baseline.

But for DBP, the treatment-induced reduction in 24-h DBP was significantly related to the baseline 24-h DBP values and the reductions in the corresponding clinic values, but it had no significant relationship with baseline clinic DBP.

TABLE 3

Multiple Regression Analysis: Determinants of Treatment-induced Reduction in Ambulatory SBP and DBP

| | β | *P* |
|---|---|---|
| Dependent Variable: Reduction in 24-h SBP | | |
| Adjusted $r^2$=0.28, *P*<0.0001 | | |
| Baseline Clinic SBP | 0.32 | 0.0007 |
| Baseline 24-h SBP | -0.40 | <0.0001 |
| Reduction in Clinic SBP | 0.42 | <0.0001 |
| Dependent Variable: Reduction in 24-h DBP | | |
| Adjusted $r^2$=0.29, *P*<0.0001 | | |
| Baseline Clinic DBP | 0.25 | 0.0860 |
| Baseline 24-h DBP | -0.39 | 0.0020 |
| Reduction in Clinic DBP | 0.50 | <0.0001 |

The possible influence of the difference between baseline CBP and ABP values on the different magnitude of their reduction under treatment was explored by analysis of covariance (Table 4), taking baseline CBP and ABP values as covariates of blood pressure reduction by treatment. Even after account had been made for the CBP and ABP values at baseline, the difference between the treatment-induced reductions in CBP and ABP remained significant (*F*=81.68, *P*<0.0001, for SBP and *F*=62.06, *P*<0.0001, for DBP).

TABLE 4

Analysis of Covariance: The Possible Influence of the Differences Between Baseline CBP and ABP Values on the Different Magnitude of Their Reduction Under Treatment

| | *F* | *P* |
|---|---|---|
| Dependent Variable: Changes in Clinic SBP | | |
| Treatment | 8.40 | <0.0001 |
| Baseline Clinic SBP | 9.51 | 0.0026 |
| Baseline 24-h SBP | 0.01 | 0.9376 |
| Difference Between Changes in Clinic and 24-h SBP | 81.68 | <0.0001 |
| Dependent Variable: Changes in Clinic DBP | | |
| Treatment | 4.54 | 0.0008 |
| Baseline Clinic DBP | 3.71 | 0.0564 |
| Baseline 24-h DBP | 0.06 | 0.8023 |
| Difference Between Changes in Clinic and 24-h DBP | 62.06 | <0.0001 |

## DISCUSSION

The advantages of ABPM over conventional blood pressure values determined at the clinic have been established previously[5-7]. Furthermore, ABPM shows a closer correlation with target organ damage, cardiovascular risk and long-term prognosis, while it seems to be particularly useful for defining the efficacy of antihypertensive medication in clinical trials[9].

The present study had two major findings. Firstly, the reduction in 24-h ABP was smaller than the concomitant reduction in CBP, the difference being substantial for the effect of antihypertensive drug treatment on the average blood pressure changes computed by considering all patients as a whole. Secondly, 24-h and CBP values were correlated both before and during treatment, the former remaining noticeably smaller than the latter in both circumstances. Thus there was a concordance between treatment effect on CBP and ABP, when one blood pressure reduction was significant. However, one should not use the definition of ‘responder’ derived from the reduction in CBP to define an ABP ‘responder’, because changes in 24-h blood pressure were substantially less than changes in CBP.

It is difficult to compare our results with those derived from previous trials[11-16] because of different study populations and design. Chatellier[10] studied the predictive value of one baseline daytime treatment according to the 1989 World Health Organization (WHO)/International Society of Hypertension guidelines for the management of mild hypertension, concluding that the predictive value of ABP, that was a diastolic ABP of two standard deviations above age-specific values in normotensive volunteers, was too low to detect with confidence those patients who need treatment according to the guidelines. Mancia *et al.*[11] had performed a meta-analysis to investigate the relationships between CBP and ABP in response to antihypertensive treatment. They found that the reduction in 24-h blood pressure was almost invariably smaller than the concomitant reduction in CBP, with the difference being substantial for the effect of antihypertensive drug treatment on the average blood pressure changes computed by considering all trials. Stergiou *et al.*[12] investigated whether BP measurement by ABP monitoring is a reliable alternative to the traditional strategy for the diagnosis of hypertension based on BP measurement on repeated clinic visits over 8 weeks. Difference between CBP and ABP was observed among 27% of the patients. White *et al.*[13] reported that the blood pressures taken in the office were substantially greater than the 24-h average blood pressures and ABP during work or at home

(awake). The present results are in agreement with the general conclusion that baseline ABP and follow-up CBP do not identify the same patients for the initiation of antihypertensive treatment or as having sustained hypertension.

The present study together with previous studies[14-15] demonstrated that the actual values of a mean 24-hour BP were different from what was assumed by the clinic BP in hypertensive individuals. The reason may comprise 3 factors: the physician's ability to determine softer Korotkoff sounds at phase V[16]; the pressor response associated with the patient's presence in the medical care environment[17] and the large reduction in BP during sleep. Additional possible reason was that the effect of drug treatment on 24-h blood pressure is not enhanced by a placebo-induced hypotension or by attenuation of a white-coat effect as compared to what occurs for CBP[7]. When using CBP measurements alone, investigators may overestimate baseline blood pressure values and the 'efficacy' of a treatment, due to a 'white-coat' effect, its subsequent attenuation and the well-known interference with this conventional blood pressure reading by a placebo effect[18]. It may be reflected from the fact that, being an average of several measurements, 24-h blood pressure does not undergo a regression to the mean phenomenon, its range in a population being much smaller than that of CBP[16].

A number of limitations have to be considered in regard to the present findings. The study was based on a small number of hypertensive patients in China. All analyses were only derived from the 8 weeks of follow-up. The results are likely to differ in other patient populations or with a longer follow-up period[19]. At present, the 'ideal' approach for evaluating blood pressure associated with administration of antihypertensive drugs over 24 h, and their impact on cardiovascular risk of patients with high blood pressure, still requires further research.

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