Does Blood Pressure Variability Affect Hypertension Development in Prehypertensive Patients?

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BACKGROUND

Blood pressure variability (BPV) is associated with end organ damage and cardiovascular outcomes in hypertensive patients. Prehypertensive patients frequently develop hypertension (HT). The purpose of the present study was to evaluate the effect of BPV on the development of HT.

METHODS

Two hundred and seven prehypertensive patients from the Cappadocia cohort were monitored over 2 years, and 24-hour ambulatory blood pressure monitoring (ABPM), office BP, and home BP measurements were subsequently performed at 4- to 6-month intervals. BPV was calculated as average real variability (ARV) from 24-h ABPM data, home BP, and office BP measurements at first visit. The relationship was evaluated between baseline ARV and the development of HT.

RESULTS

HT was diagnosed in 25.60% of subjects. Baseline 24-hour ABPM systolic blood pressure $(SBP)_{ARV}$ and diastolic blood pressure $(DBP)_{ARV}$ and home SBP_{ARV} were significantly higher in patients who developed HT than the other patients (*P* 0.006, 0.001 and 0.006, respectively). Baseline 24-hour ABPM SBP_{ARV} and home SBP_{ARV} exceeding the 90th percentile were identified as parameters affecting development of HT at logistic regression analysis.

CONCLUSION

In conclusion, our prospective observational cohort study showed that short-term BPV in particular can predict the development of HT in the prehypertensive population.

Keywords: blood pressure; hypertension; Blood pressure variability; prehypertension; BPV; 24h-ABPM.

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Hypertension (HT) is the principal risk factor among preventable causes of death, with a growing global prevalence. Diagnosis of HT was for long based on office blood pressure (OBP) measurements. Powerful evidence exists of a direct relationship between OBP and cardiovascular events, renal outcomes, and general mortality.[1,2] However, the potential role of blood pressure variability (BPV) from the data obtained using out-of-office blood pressure measurements methods has increased in recent years.[3,4]

BPV refers to fluctuations in the course of BP as a result of complex interactions of various environmental and individual factors mediated by cardiovascular regulatory mechanisms (humoral, neural, etc.). BP fluctuates throughout the day during various physiological events, such as inspiration–expiration, and sleep-waking periods.[3] Significant variations in BP outside the limits of physiological BP fluctuation are interpreted as BPV. BP values can vary from beat to beat, minute to minute, hour to hour, and day to night over a 24-hour period, and these variations are known as short-term BPV. Differences in BP measurements on different days are known as midterm BPV, and differences between different weeks, months, or even years are referred to as long term.[5] BPV can be measured using several methods. SD, coefficient variant (CV), smoothness index (SI), and average real variability (ARV) can be calculated from 24-hour ABPM, office BP, and home BP measurements.[5–7] However, there is insufficient evidence to show which measurements (office, home, or 24-hour ABPM) of BPV and which method (SD, ARV, CV, SI, etc.) are more predictive. Numerous studies have shown that an increase in short- or long-term BPV associated with hypertensive organ damage and cardiovascular risk independently of OBP and is associated with cardiovascular outcomes.[8–10]

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Although various different numerical ranges and nomenclatures have been used for pre-HT during the historical process, this is generally the name given to patients remaining between optimal BP and stage 1 HT BP values. This group is distinguished from individuals with optimal BP by more frequent HT development and cardiovascular morbidity and mortality.[11–13]

The purpose of this prospective cohort study was to determine whether baseline BPV can predict the development of HT in the prehypertensive patient.

METHODS

The Cappadocia cohort is a prospective cohort study that commenced in March 2013 and is being closely observed by the Turkish Society of Internal Medicine. The study design and protocol have been previously described elsewhere.[14,15] Briefly, at the start of the cohort, all participants underwent detailed physical examinations including BP (at least twice), body weight, and height measurements. BP at the time of enrollment in the cohort was measured as recommended in Joint National Committee (JNC) Guideline 7 (JNC 7).[16] All members of the cohort are monitored on an annual basis in terms of alterations in these parameters, onset of new diseases, variations in weight or waist circumference, receipt of medication, tobacco and alcohol use, and diet. In addition, all patients were informed about lifestyle changes for HT prevention and control, both at the start of the cohort (March 2013) and throughout the study for ethical reason.

Patient selection

The Cappadocia cohort pre-HT follow-up study started 2 years after the beginning of the cohort follow-up (January 2015). Prehypertensive individuals from the 5,150 members of the Cappadocia cohort identified on the basis of 2 OBP measurements in 2013 were randomly invited to participate to the study. Two hundred and seven of 327 volunteer participants met the inclusion criteria at the first office visit and were enrolled in the study (Figure 1). Individuals aged over 18, meeting the inclusion criteria, and giving both written and verbal consent were included in the study. Pregnant women, individuals with known heart failure, kidney failure, or chronic liver disease, or using antihypertensive drugs, and those unwilling to participate were excluded. Ethical committee approval was granted by the Hacettepe University Medical Faculty, Turkey. The study has started once informed written consent had been obtained from all participants.

Study protocol

The 207 individuals consenting to participate in the study, based on BP measurements performed during inclusion in the cohort 2 years previously, were selected in accordance with the JNC 7 guideline. All subjects enrolled in the study underwent detailed physical examinations after their demographic data had been recorded at the first control. OBP was measured as described in the JNC 7 guideline.[16] Home BP measurements were performed for a week, after which all patients underwent 24-hour ABPM. All 3 BP measurements—office, home, and 24-hour ABPM—were repeated at 4- to 6-month intervals during the follow-up. HT was diagnosed in case of an OBP measurement ≥ 140/90 mm Hg, and a 24-hour ABPM all-day average ≥ 130/80 mm Hg, and/or a home BP measurement ≥ 135/85 mm Hg. Pre-HT was defined as OBP values of 120–139/80–89 mm Hg. Patients with HBPM < 135/85 mm Hg and mean daytime 24-hour ABPM < 130/80 mm Hg despite office BP measurements ≥ 140/90 mm Hg throughout the study were regarded as white coat HT (WCHT), and patients with office BP measurement < 140/90 mm Hg and HBPM ≥135/85 mm Hg and/or mean daytime 24-hour ABPM ≥ 130/80 mm Hg were regarded as masked HT.[16] Patients in whom HT was detected at any visit were referred to family medicine practitioners for treatment. All patients

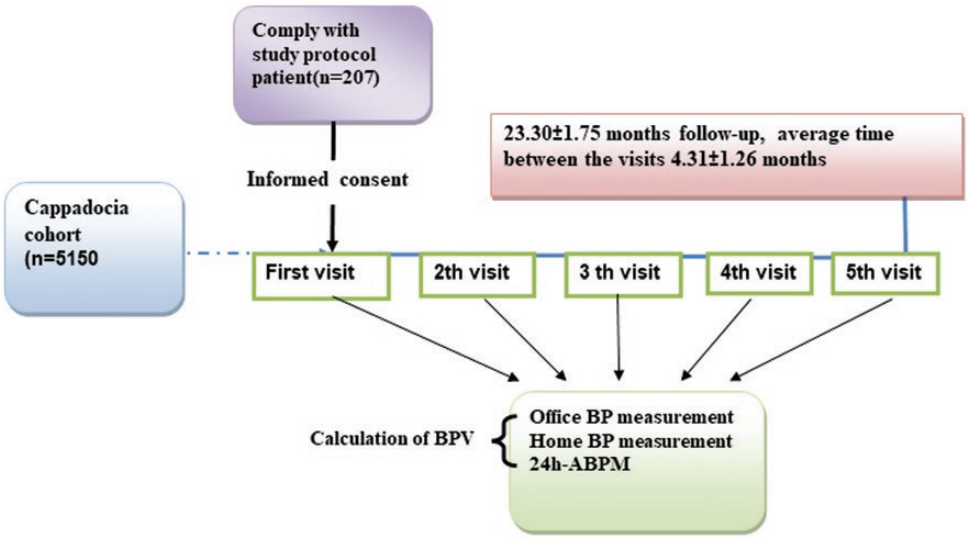

Figure 1. Flow chart of the study protocol.

were informed about lifestyle changes, both at the start of the cohort and throughout the study.

BP measurement methods

Office blood pressure measurement A validated UA-651SL monitor (A&D Company,1–243 Asahi, Kitamoto-shi, Saitama-ken, Japan) device was employed to measure OBP. This was done as described in the JNC 7 guidelines.[16] Before the procedure, all patients were asked to rest for at least 5 min in a relaxed position in a quiet room at a comfortable temperature. BP was measured by a physician from both arms using a cuff of a suitable size for the patient's upper arm, with the upper arm held at heart level, with the back and the upper arm supported, and with the patient sitting upright. We were careful to ensure that patients did not cross their legs or speak during the procedure. Once BP had been measured from both arms, subsequent BP measurements were carried out using the arm eliciting the highest value. BP was measured 5 times at 1-minute intervals. The first value obtained was excluded from the analysis, while the mean of the 4 subsequent values obtained was recorded as OBP. The same procedure was employed to measure OBP at every 4–6 monthly visit.

Home blood pressure measurement Home BP was determined using a UA-651SL monitor (A&D Company,1–243 Asahi, Kitamoto-shi, Saitama-ken, Japan). Patients were first instructed for the appropriate technique and then measured their own home BP. This was measured 5 times at 1-minute intervals in the mornings and evenings over a 1-week period. Mean morning and evening values were calculated at the end of that time and recorded as home BP values. The same procedure was employed to measure home BP at each subsequent 4–6 monthly visit. Blood pressure devices for use at home were randomized at each control on order to avoid device-related bias.

Ambulatory blood pressure measurement Twenty-four-hour ABPM measurement was performed using a Mobil-O-Graph NG 24h ABPM Classic (I.E.M. GmbH, Stolberg, Germany) device. Daytime BP measurement was carried out every 15 minutes and nighttime measurement every 30 minutes. Subjects achieving a minimum 70% measurement in 24-hour ABPM records were included in the analysis.[17] Patients were asked to record the amounts of time they spent sleeping, waking and eating, as well as daily activities performed. Sleeping and waking periods were calculated on the basis of these data. They were also asked to ensure that the relevant arm remained still during measurement. The same procedure was subsequently employed at every 4–6 monthly visit, and the ABPM devices were also randomly allocated for the patients.

BPV assessment BPV determinants were calculated for both systolic and diastolic BP using ARV of all 3 techniques (24-hour ABPM, home, and office).

ARV values were calculated from baseline 24-hour ABPM, home, and office measurements using the following formula:

$$\mathrm{ARV} = \frac{1}{N-1}\sum_{k=1}^{N-1}|\mathrm{BP}_{k+1} - \mathrm{BP}_k|$$

where N represents the total number of valid BP measurements, and BP k+1and BP k represent 2 consecutive BP measurements.[7]

ARV in Home BP measurements was calculated by sequential listing and formulating 7-day morning and evening BP measurements.

Statistical analysis

PASW 18.0 for Windows software was employed for statistical analysis. Descriptive statistics were expressed as number and percentage for categorical variables and as mean, SD, median, minimum, maximum, and 25th and 75th percentiles for numerical variables. Variables' compatibility with normal distribution was evaluated using visual (histograms and probability charts) and analytical (Kolmogorov–Smirnov/Shapiro–Wilk tests) methods. The chi-square test was employed in 2-way and multiple group comparisons of categorical variables when chi-square conditions were met, and Fisher's exact test when these were not met. Friedman's test was applied for repeated measurement analysis for numerical variables when normal distribution conditions were not met. The Mann–Whitney U test was employed in 2-way group comparisons for numerical variables, and the Kruskal–Wallis test in multiple group comparisons. Logistic regression analysis was used to determine possible independent predictors of HT. In the logistic regression analysis, parameters that were significant in univariate analysis and parameters that we thought could predict the development of HT were included. Body mass index (BMI), age, gender, and ARV were included in the logistic regression analysis. Pearson's correlation analysis was applied for correlation analysis. P values less than 0.05 were considered statistically significant.

RESULTS

The 207 prehypertensive patients (median age 50, 62.3% women) were followed up for a mean 23.30 ± 1.75 months at mean intervals of 4.31 ± 1.26 months. At the end of this period, 76 individuals became normotensive, whereas 49 individuals remained prehypertensive. HT developed in 53 individuals, masked HT in 23 individuals, and WCHT in 6 individuals.[15] We thought that some of our patients were became normotensive due to lifestyle changes advice from the start of cohort.

Table 1 shows a comparison of demographic parameters in patients developing HT and other patients. Table 2 shows that the baseline $\mathrm{SBP}_{\mathrm{ARV}}$ and $\mathrm{DBP}_{\mathrm{ARV}}$ calculated from initial 24-hour ABPM data were significantly higher in people who developed HT than in the other cases (prehypertensive, masked HT, WCHT, and normotensive) (P = 0.001 and <0.001, respectively).

Correlation analysis of parameters affecting baseline BPV revealed weak positive correlation between 24-hour ABPM

SBP_{ARV} and age ($R = 0.214$, $P < 0.05$) and BMI ($R = 0.167$, $P < 0.05$), whereas 24-hour ABPM DBP_{ARV} exhibited weak positive correlation only with BMI ($R = 0.178$, $P < 0.05$). Home SBP_{ARV} was weakly positively correlated with age ($R = 0.214$, $P < 0.05$) and BMI ($R = 0.1178$, $P < 0.05$).

At logistic regression analysis, 24-hour ABPM SBP_{ARV} ($P = 0.003$, odds ratio: 4.22, 95% confidence interval 1.639–10.86) and home SBP_{ARV} ($P = 0.049$, odds ratio: 3.90, 95% confidence interval 1.008–15.13) exceeding the 90th percentile were identified as factors affecting development of HT.

DISCUSSION

In this observational cohort study, initial BPV values were significantly higher in the group who developed HT compared to other cases (prehypertensive, masked HT, WCHT, and normotensive). In addition, 24-hour ABPM SBP_{ARV} and home ARV-SBP_{ARV} exceeding the 90th percentile were identified as parameters affecting whether individuals would become hypertensive.

Previous clinical studies have shown that BPV is associated with asymptomatic end organ damage. In the first study by Parati *et al.* 24-hour intra-arterial BP monitoring, using the Oxford method, was performed on 108 hospitalized essential HT patients and they had detected greater asymptomatic organ damage in patients with high 24-hour BPV.[8] Frattolla *et al.* later followed up 73 HT patients for 7.4 years and showed that initial 24-hour BPV was closely associated with end organ damage, particularly left ventricular hypertrophy.[18] Studies in later years showed that short-term BPV is associated with damage in several end organs, such as carotid artery damage, left ventricular hypertrophy, and renal function disorder.[19–21] In our previous study performed in our own clinic, we showed a link between soluble endothelial protein C, a procoagulant molecule, and 24-hour ABPM SBP_{ARV}, in 51 newly diagnosed HT patients.[22] Numerous studies have also shown that visit-to-visit BPV (long-term BPV) is associated with endothelial dysfunction, carotid atherosclerosis, proteinuria, and cognitive function impairment.[23,24] Studies investigating the place of short-term BPV in predicting cardiovascular events have yielded inconsistent results. Although high initial 24-hour BPV has been reported to increase the development of cardiovascular events and mortality in the majority of studies,[25,26] others have reported a limited effect in predicting cardiovascular event development.[9] A large number of meta-analyses and studies have reported that visit-to-visit BPV predicts cardiovascular outcomes better than short-term BPV, especially in HT patients receiving treatment.[10,27,28] In the light of the existing literature, short- and long-term BPV appear to be clearly associated with end organ damage and cardiovascular event damage. However, our review of the literature revealed no studies investigating the place of BPV in predicting HT development in the normotensive and/or prehypertensive population. We think that our study can play a leading role in the elucidation of this subject. This is because the SBP_{ARV} and DBP_{ARV} obtained from baseline 24-hour ABPM and home measurements were significantly higher in the group who developed HT compared with other patients. Additionally, we identified initial 24-hour ABPM SBP_{ARV} and home SBP_{ARV} as predictors of HT development in the prehypertensive patient group. We think that, based on our study results, short-term BPV calculated from 24-hour ABPM and home BP measurements from the first control in the prehypertensive group can be interpreted as a predictor of HT development. In particular, the fact that BPV calculated from home BP measurements is of assistance in predicting HT development may represent a very useful predictor for patients in whom 24-hour ABPM is not possible.

Numerous studies have shown that HT develops more frequently in prehypertensive patients than in normotensive individuals and that cardiovascular events also occur more frequently in the former group.[11–13] HT guidelines have therefore recommended that the prehypertensive patient groups should be more closely monitored than normotensive individuals and that if necessary, out-of-office BP measurements should be performed to test for the presence of masked HT, which is more frequently seen in this patient group.[17]

Factors predicting the development of HT in the prehypertensive group are also under investigation. The majority of studies to date have shown that classic cardiovascular risk factors, and particularly age, increased BMI, and ethnic

Table 1. Comparison of demographic and biochemical parameter in patients developing hypertension and other patients

	Hypertension	Other	*P* value
Gender: *n* (%), Female	34 (64.2)	95 (61.7)	NS
Age (year)	51.3 ± 7.9	49.5 ± 8.2	NS
Body mass index (kg/m^2)	31 ± 4.51	29.57 ± 5.07	0.026
Office SBP (mm Hg)	136.68 ± 14.14	117.75 ± 10.62	<0.001
Office DBP (mm Hg)	85.46 ± 9.06	75.78 ± 7.77	<0.001
Home SBP (mm Hg)	127.25 ± 10.82	112.51 ± 9.34	<0.001
Home DBP (mm Hg)	77.51 ± 7.3	70.95 ± 6.56	<0.001
24-h ABPM all-day SBP (mm Hg)	131.58 ± 10.24	116.19 ± 9.68	<0.001
24-h ABPM all-day DBP (mm Hg)	82.36 ± 6.96	73.11 ± 7.46	<0.001

Other group includes prehypertensive, normotensive, white coat hypertension, and masked hypertension. Abbreviations: ABPM, ambulatory blood pressure monitoring; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 2. Comparison of baseline blood pressure variability indices in hypertensive and other groups

	Hypertension	Masked HT	Prehypertensive	WCHT	Normotension	*P* value
24-h ABPM SBP_{ARV}	12.33 ± 3.83	11.13 ± 3.96	10.91 ± 3.04	9.87 ± 1.03	9.95 ± 2.37	0.006
24-h ABPM DBP_{ARV}	10.20 ± 2.44	8.80 ± 2.30	9.09 ± 2.81	7.66 ± 1.19	8.48 ± 2.13	0.001
Home SBP_{ARV}	7.19 ± 1.75	6.59 ± 1.98	6.28 ± 2.08	5.72 ± 1.79	6.13 ± 1.77	0.006
Home DBP_{ARV}	4.61 ± 1.20	4.43 ± 1.19	4.71 ± 1.52	3.54 ± 1.59	4.52 ± 1.49	NS
Office SBP_{ARV}	7.19 ± 1.75	5.67 ± 2.56	5.82 ± 3.48	8.71 ± 3.72	6.14 ± 3.59	NS
Office DBP_{ARV}	4.61 ± 1.20	3.48 ± 2.48	4.25 ± 2.49	4.21 ± 2.74	4.61 ± 2.97	NS

Abbreviations: ABPM, ambulatory blood pressure monitoring; DBP, diastolic blood pressure; HT, hypertension; SBP, systolic blood pressure; WCHT, white coat HT.

origin, contribute to HT development.[29,30] BMI values in the present study were high in both the population developing HT and the population with no such development, and were also compatible with the data from a previous HT prevalence study from Turkey.[31] However, the results of this study show that 24-hour ABPM SBP_{ARV} and home SBP_{ARV} predict HT development in prehypertensive patients, but that age, BMI, and gender are not predictive.

There are a number of weaknesses and limitations to this study. The limited number of prehypertensive patients, and therefore of patients developing HT, prevents us from reaching a definite conclusion concerning the place of BPV in predicting HT. In addition, our 2-year follow-up period also led to a low number of newly diagnosed HT cases. However, particular strengths of this study include its cohort nature, the fact that office and out-of-office BP measurements were monitored every 4- to 6 months.

In conclusion, this prospective, observational cohort study shows that short-term BPV in particular is capable of predicting the development of HT, in the prehypertensive population. We think that individuals with high BPV in this high-risk group should be more closely followed up in terms of HT development.

CLINICAL PERSPECTIVE

What Is New?

(1) The current study demonstrates that baseline 24-hour ambulatory blood pressure monitoring (ABPM) systolic blood pressure $(SBP)_{ARV}$ and diastolic blood pressure $(DBP)_{ARV}$ and home SBP_{ARV} were significantly higher in patients who developed hypertension (HT) than in the non-HT population.
(2) We also found that baseline 24-hour ABPM SBP_{ARV} and home SBP_{ARV} exceeding the 90th percentile were identified as parameters affecting development of HT.

What Are the Clinical Implications?

(1) Short-term blood pressure variability (BPV) calculated from 24-hour ABPM and home BP measurements from the first control in the prehypertensive group can be interpreted as a predictor of HT development. We think that individuals with high BPV in this high-risk group should be more closely followed up in terms of HT development.

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DISCLOSURE

The authors declared no conflict of interest.

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