Original Article

Estimation of Base Blood Pressure by Using a New Device in the Outpatient Clinic

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Direct measurement of intra-arterial blood pressure (BP) for 24-h provides approximately 100,000 values that vary enormously, but each (BP_i) can be expressed by the equation $BP_i = BP_0 + \Delta BP_i$ (BP_0 , base BP; ΔBP_i , BP increment, $i=1, 2, \dots, 100 \times 10^3$). About 20% of outpatients with hypertension exhibit white-coat hypertension (WCH). In such patients, ΔBP_c ($i=c$; c, time at the clinic) is surmised to be large. A method for explaining the physiological factors in ΔBP_c and the estimation of base BP in the outpatient clinic is important. This study addresses this issue. A total of 293 subjects were divided into four groups: 1) WCH group, 45 individuals (office BP $\geq 140/90$ mmHg and 24-h indirect BP $< 125/80$ mmHg); 2) normotensive (NT) group, 84 controls matched for age and sex; 3) WHO-I group, 95 hypertensive patients with WHO stage I (office BP $\geq 140/90$ mmHg and 24-h BP $\geq 125/80$ mmHg); and 4) WHO-II group, 69 hypertensive patients with WHO stage II. Their BP_c and heart rate (HR; HR_c , clinic HR) values were measured by a BP-ECG monitoring device in the outpatient clinic. Power-spectral analysis was used to obtain the ratio between the low-frequency component (LF) and high-frequency component (HF) of ECG-RR variability ($LF/HF=LH$). Twenty-four-hour indirect BP (and BP_0) and base HR (HR_0) were measured by a portable device (TM2425) at 30-min intervals. Then, $\Delta BP_c (=BP_c - BP_0)$ was estimated by performing linear multivariate analysis applying the model equation $\Delta BP_c = (BP_c - \alpha LH)(1 - \beta HR_0/HR_c) + \varepsilon$ to the above variables (α and β , constant values; ε , error). This model equation made it possible to estimate BP_0 (and ΔBP_c) with a high coefficient of correlation ($r \geq 0.85$, mean of error less than 0.82 ± 5.9 mmHg). The predictive accuracy for discrimination between WCH and sustained hypertension (WHO-I and WHO-II groups) by this equation was 88%. The new ΔBP -estimation device (BP-ECG monitor) enabled us to infer BP_0 and is therefore useful in estimating WCH in the outpatient clinic. (*Hypertens Res* 2006; 29: 233–241)

Key Words: white-coat hypertension, ambulatory blood pressure monitoring, sympathetic nervous system, baroreflex

Introduction

As ambulatory blood-pressure (BP) monitoring and home BP monitoring methods are now being used in ordinary clinics, the difference between BP measured with these methods and office (clinic) BP measurements is becoming an issue (1, 2). In addition, various studies are producing diverse findings in connection with white-coat hypertension (1) (isolated clinic

hypertension (3)), reverse white-coat hypertension (4), masked hypertension (5), and non-dipper (6), inverted dipper (7), and extreme dipper (8) types. Under these circumstances, clinicians may be confused as to which BP values to use in diagnosing patients and determining therapy. Smirk *et al.* (9) have suggested that basal BP is useful in diagnosing hypertension. Basal BP is defined as the minimum BP measured early in the morning in the bedroom after a night of deep sleep induced the previous day by administration of pentobarbi-

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Received August 23, 2005; Accepted in revised form January 13, 2006.

Fig. 1. Automatic blood pressure (BP) and LF/HF (LH) monitoring device in an outpatient clinic. LF/HF, the ratio of low-frequency component (LF)/high-frequency component of ECG-RR variability (HF); HR_0 , base heart rate (HR); SBP_c / DBP_c , systolic BP and diastolic BP in the clinic; SBP_0' / DBP_0' , estimated base SBP and DBP.

tone. The basal BP is closely related to hypertension severity and mortality (9). Subtracting basal BP from casual BP gives the supplemental BP, which has no correlation with hypertension severity or prognosis (9).

In a similar way, we can also employ the minimum sleep-time BP (base BP) (10–13), which is highly reproducible and closely connected to the severity of hypertensive organ damage (10, 11, 13). Staessen *et al.* (14) reported a close relation between nighttime BP and cerebral and cardiovascular events, leading to the idea that whether basal BP (base BP or nighttime BP) is high plays an important part in diagnosing and treating hypertension.

The present study deals with methods for estimating base BP in the outpatient clinic while measuring clinic (casual) BP (BP_c) and with methods for evaluating the difference between BP_c and base BP (ΔBP_c ; $\Delta BP_c = BP_c - BP_0$). The white-coat effect may be evaluated in the following ways: by taking the difference between BP_c and BP measured in the home (15), by taking the difference between BP_c and mean daytime BP (16, 17), and by taking the difference between BP_c measured by a physician and BP measured while the subject is relaxed (18, 19). The approximately 100,000 values for 24-h intra-arterial BP measured directly vary enormously, but each (BP_i) can be expressed by the equation $BP_i = BP_0 + \Delta BP_i$ (BP_0 , base BP; ΔBP_i , BP increment, $i = 1, 2, \dots, 100 \times 10^3$), and day-to-day variation in BP_0 is small (10). Since we consider base BP (BP_0) to be a stable value on which the environment exerts minimal influence, we analyzed the difference between BP_c and base BP ($\Delta BP_c = BP_c - BP_0$) and use ΔBP_c for estimation of white-coat hypertension in the outpatient clinic.

Fig. 2. Correlations between $\Delta SBP/SBP_c$ and $\Delta HR/HR_c$ and between $(\Delta SBP/SBP_c)/(\Delta HR/HR_c)$ and LH/SBP_c . SBP , systolic blood pressure; ΔSBP_c , the difference between clinic (office) SBP (SBP_c) and base SBP (SBP_0); HR , heart rate; ΔHR , difference between clinic HR (HR_c) and base HR (HR_0); LH , ratio of LF/HF; LF/HF, low frequency component/high frequency component of ECG-RR variability (power spectral analysis).

Methods

The basis of the working hypothesis for estimating BP_0 in the outpatient clinic is as follows. First, past research (20) has shown that in instances of the white-coat phenomenon, heart rate (HR) increases. Our own work (21) has shown a strong correlation between fluctuations of HR and BP over a 24-h period in normotensive individuals and patients with mild or moderate essential hypertension. When the difference between clinic systolic BP (SBP_c) and base systolic BP (SBP_0) is expressed as ΔSBP ($=SBP_c - SBP_0$) and the difference between clinic HR (HR_c) and base HR (HR_0) is expressed as ΔHR ($=HR_c - HR_0$), the ratio of BP fluctuation ($\Delta SBP/SBP_c$) and the ratio of HR fluctuation ($\Delta HR/HR_c$) correlate. From this relationship, it becomes possible to estimate ΔSBP to an extent.

Second, the baroreflex control system, one of the functions

regulating BP, influences the relation between $\Delta\text{SBP}/\text{SBP}_c$ and $\Delta\text{HR}/\text{HR}_c$. Possibly, when ΔSBP rises beyond the level suitable for target organ blood flow, a mechanism inhibiting sympathetic nervous activity (SNA) goes into action (22, 23). Grassi *et al.* (24) too observed inhibition of muscle SNA in individuals with the white-coat effect. As long as baroreceptor sensitivity is preserved, rises in $\Delta\text{SBP}/\text{SBP}_c$ unsuitable in connection with rises in $\Delta\text{HR}/\text{HR}_c$ ($[\Delta\text{SBP}/\text{SBP}_c]/[\Delta\text{HR}/\text{HR}_c]$) are thought to cause a decrease in SNA/SBP_c , producing negative feedback. Because SNA such as muscle SNA is hard to measure in the outpatient clinic, the ratio between the low-frequency component (LF) and high-frequency component (HF) (LF/HF, abbreviated as LH) of HR variability (a marker of SNA (25)) can be used to derive this hypothetical equation ($\propto$, proportional):

$$(\Delta\text{SBP}/\text{SBP}_c)/(\Delta\text{HR}/\text{HR}_c) \propto -\text{LH}/\text{SBP}_c. \quad (1)$$

As a result of observing the negative correlation between its left and right sides (Figs. 1 and 2), we are able to express Eq. (1) as follows:

$$(\Delta\text{SBP}/\text{SBP}_c)/(\Delta\text{HR}/\text{HR}_c) \propto 1 - \text{LH}/\text{SBP}_c.$$

Taking ε to represent the margin of error and α and β as constants, we arrive at the following equation ($\Delta\text{HR}/\text{HR}_c = 1 - \text{HR}_0/\text{HR}_c$):

$$\Delta\text{SBP} = \text{SBP}_c(1 - \alpha \cdot \text{HR}_0/\text{HR}_c)(1 - \beta \cdot \text{LH}/\text{SBP}_c) + \varepsilon. \quad (2)$$

Equation (2) then becomes:

$$\begin{aligned} \text{SBP}_c - \text{SBP}_0 &= \text{SBP}_c - \alpha \cdot \text{SBP}_c \cdot \text{HR}_0/\text{HR}_c \\ &\quad - \beta \cdot \text{LH} + \alpha\beta \cdot \text{LH} \cdot \text{HR}_0/\text{HR}_c + \varepsilon \\ \text{SBP}_0 &= \alpha \cdot \text{SBP}_c \cdot \text{HR}_0/\text{HR}_c + \beta \cdot \text{LH} \\ &\quad - \alpha\beta \cdot \text{LH} \cdot \text{HR}_0/\text{HR}_c - \varepsilon. \end{aligned} \quad (3)$$

This SBP_0 equation takes $\text{SBP}_c \cdot \text{HR}_0/\text{HR}_c$, LH, and $\text{LH} \cdot \text{HR}_0/\text{HR}_c$ as variables. Therefore, we thought it possible to estimate base systolic BP (SBP_0') from the coefficients (α , β , ε) derived from actual measurement values. Similarly, to infer base diastolic BP (DBP_0') from clinic diastolic BP (DBP_c), we used DBP_c instead of SBP_c in Eq. (3), and, using actual measurement values (DBP_0 , $\text{DBP}_c \cdot \text{HR}_0/\text{HR}_c$, LH and $\text{LH} \cdot \text{HR}_0/\text{HR}_c$), performed linear multivariate regression analysis on these variables.

BP-ECG Monitor

This device is used to estimate base BP from four factors: BP_c , HR_c , HR_0 and LH during office BP measurement (Fig. 1). A commercial device for measuring BP and recording an ECG (TM2562, A&D Co., Ltd., Tokyo, Japan) used in conjunction with a personal computer (PC) for analyses made it possible to measure these factors simply and quickly in outpatients and to display calculation results for SBP_0' and DBP_0' : estimated values for base BP (Fig. 1).

For LH, power-spectral analysis (25, 26) using the autoregressive model, on which we have already reported, of ECG-RR variability for 5 min was performed. Computer calculations were made of LF (0.05–0.15 Hz), HF (0.15–0.4 Hz), and LH. The mean of HR values in 5-min intervals was used for HR_c .

The oscillometric method was used to measure SBP_c and DBP_c , and means were taken of two measurements made before and after 5-min LH measurements. These measurements with this device were performed between 10:00 and 12:00 and between 13:00 and 16:00, with the subjects seated. They were not permitted to smoke or ingest caffeine for 30 min beforehand. It was ascertained that their bladders were not full. HR_0 was measured with a Holter ECG or HR recorder (wristwatch type) according to a method we have previously reported (27).

Ambulatory BP Measurement

The portable multi-biomedical recorder (25) (TM2425, A&D Co., Ltd.) we used records indirect BP by the cuff oscillometric method for 24 h at 30-min intervals. Its BP accuracy has been validated by and satisfies the criteria of the Association for the Advancement of Medical Instrumentation (AAMI protocol). Nighttime (sleep-time) data were derived from the subjects' diaries. Because such factors as depth of sleep and rapid eye movement (REM) sleep influence BP, it is impossible to be certain that nighttime BP readings represent true sleep-time BP. Therefore, we took minimum sleep-time BP (base BP) as the representative sleep-time BP (10). TM2425 data and computer analysis have shown base BP to correspond statistically to minimum sleep-time HR (10).

Subjects

The subjects were 209 hypertensive patients (103 men and 106 women) and 84 normotensive volunteers (NT-group; 41 men and 43 women) ranging in age from 25 to 75 years. BP measured by the auscultatory method in the office 3 times on 3 different days was ≥ 140 mmHg for SBP or ≥ 90 mmHg for DBP (Korotkoff phase V) in the hypertensive patients. SBP was < 130 mmHg and DBP < 85 mmHg in the age-matched normotensive subjects (mean age 53 ± 18 years). The hypertensive patients were on no medication. After routine examinations, only individuals with World Health Organization (WHO) stage I (WHO-I) or II (WHO-II) essential hypertension (28) were selected for the study.

WHO-I patients showed no objective signs of hypertensive organ damage. Their chest X-rays showed a cardio-thoracic ratio (CTR) of $< 50\%$. The sum of SV_1 and RV_5 on their ECG was < 4.0 mV. Echocardiographic left ventricular mass (LVM) index was < 134 g/m² for male patients and < 110 g/m² for female patients. Their Keith-Wagner-Barker (KW) ophthalmic category was lower than grade I, and their creatinine level was < 91.5 $\mu\text{mol/l}$. Patients with WHO stage I were

Table 1. Main Clinical Characteristics of Office Hypertensives Groups

Criteria	Group		
	WCH	WHO-I	WHO-II
No. (men/women)	45(21/24)	95(45/50)	69(38/31)
Age (years)	53±14	56±12	57±11
Height (cm)	159±7.9	160±8.3	162±6.4
Body weight (kg)	59±7.2	61±11	65±8.5**
CTR on chest X-ray (%)	43±3	44±3	55±4**
SV ₁ +RV ₅ (ECG) (mV)	3.4±0.5	3.6±0.8	4.3±1.2**
LVM index (g/m ²)	99±15	104±16	150±22**
Plasma creatinine (μmol/l)	75±10	78±9	85±11**
Office SBP (mmHg)	151±7.9	152±8.2	162±12.1**
DBP (mmHg)	84±21.1	89±10.4	102±9.9**
HR (beats/min)	82±8.4	76±10.0**	76±12.1**

WCH, white-coat hypertension; WHO-I, World Health Organization (WHO) stage I hypertension; WHO-II, WHO stage II hypertension; CTR, cardiothoracic ratio; SV₁+RV₅, the sum of SV₁ and RV₅ on their ECG; LVM, echocardiographic left ventricular mass; SBP, systolic blood pressure (BP); DBP, diastolic BP; HR, heart rate. ** $p<0.01$ vs. WCH.

Table 2. Twenty-Four-Hour BP, HR and LH at Outpatient Clinic

	NT	WCH	WHO-I	WHO-II
24-h SBP (mmHg)	119±9	122±7	141±8**	159±11**
DBP (mmHg)	73±8.2	76±8.6	84±7.4**	93±8.8**
HR (beats/min)	65±7.5	67±8.3	68±8.2*	71±9.3**
Base SBP (mmHg)	97±8.4	103±7.2*	116±7.7**	132±7.7**
DBP (mmHg)	56±8.1	62±6.2*	68±5.7**	78±5.8**
HR (beats/min)	50±7.0	51±5.7	53±6.5*	57±8.3**
ΔSBP (mmHg)	22±8.1	47±10.3**	37±9.7**	30±10.0**
ΔDBP (mmHg)	14±9.2	23±11.4**	22±9.3**	18±9.3**
ΔHR (beats/min)	20±8.1	31±7.1**	24±8.4**	17±8.6*
LF (ms/Hz ^{1/2})	53±31	40±26*	35±19**	35±24**
HF (ms/Hz ^{1/2})	28±16	23±15	14±10**	17±14**
LH (ratio)	2.1±0.65	1.9±0.64	2.7±0.84**	2.3±1.05

BP, blood pressure; HR, heart rate; LH, LF/HF (LF, low frequency component and HF, high frequency component of HR-power spectral analysis); SBP, systolic BP; DBP, diastolic BP; ΔSBP=(office SBP) – (base SBP); ΔDBP=(office DBP) – base DBP; ΔHR=(office HR) – (base HR); NT, normotensive group; WCH, white-coat hypertensive group; WHO-I, WHO-II, World Health Organization (WHO) stage I and WHO stage II hypertensive group, respectively. * $p<0.05$; ** $p<0.01$ vs. NT and † $p<0.01$ between WCH and WHO-I.

subdivided into two groups; a white-coat hypertension (WCH) group whose 24-h systolic BP/diastolic BP was <125/80 mmHg, and a group made up of the remaining patients (WHO-I) (24-h BP ≥ 125/80 mmHg).

WHO-II patients had left ventricular hypertrophy without retinopathy and demonstrated no cardiac, cerebral or renal complications (plasma creatinine level <152 μmol/l).

Table 1 shows patient numbers, sex, age, mean office BP

and main clinical characteristics for each hypertensive group.

The study was approved by the ethical committee of our institute, and subjects gave written informed consent.

Statistical Analysis

Standard statistical methods, including ANOVA, non-paired *t*-test, *F*-test, and least-squares linear regression analysis for

two variables were used. The Multiple Statistical Analysis Program (Social Survey Research Information Co., Ltd., Tokyo, Japan) was used for multiple least-squares linear regression analysis and discriminant analysis between the WCH-group and the sustained hypertensive groups. The discriminant function ($D_{1.2} = ax + by + c$) was determined to allocate a patient to group 2 (WCH-group), if $D_{1.2} > 0$. Predictive accuracy was calculated as: $(n_1 + n_2)/\text{total number}$; n_1 and n_2 are the numbers of patients classified accurately into each group (WCH or sustained hypertensive group). Values are expressed as the mean $\pm$ SD, and values of $p < 0.05$ were considered significant.

Results

No significant difference in 24-h BP was observed between the WCH-group and the NT-group, but base BP (BP_0) was significantly lower ($p < 0.01$) in the WCH-group than in the WHO-I group (Table 2).

ΔSBP ($= SBP_c - SBP_0$) and ΔHR ($= HR_c - HR_0$) were higher ($p < 0.01$, Table 2) in the WCH-group than in any other group. In the WCH-group, LF and HF tended to be lower than those in the NT-group, but there was no difference in LH between the two groups. LH was significantly lower ($p < 0.01$) in the WCH-group than in the WHO-I group (Table 2).

Thus, the WCH-group was characterized by higher ΔSBP and ΔHR than the NT-group, and no significant difference in LH was observed. In comparison with the WHO-I group, on the other hand, ΔHR was greater and base BP and LH were significantly lower in the WCH-group.

Consequently, HR and LH are thought to be useful factors for the diagnosis of WCH. We investigated the mutual relations among BP, HR, and LH in the outpatient clinic. In Eq. (1), a high correlation ($r = 0.69$) was observed between $\Delta SBP/SBP_c$ and $\Delta HR/HR_c$ (Fig. 2). In addition, we examined the relation between $(\Delta SBP/SBP_c)/(\Delta HR/HR_c)$ as the y -axis and LH/SBP_c as the x -axis. This analysis showed a negative correlation between the two: $y = 1.0 - 13.5x$ ($r = -0.31$, $p < 0.01$), thus providing a basis for Eq. (1) or (2) (Fig. 2). The actual measured SBP_0 was the objective (independent) variable, and $SBP_c \cdot HR_0/HR_c$, LH, and $LH \cdot HR_0/HR_c$ were the dependent variables in the multivariate analysis, giving the coefficients in Eq. (3)':

$$SBP_0' = 0.85SBP_c \cdot (HR_0/HR_c) + 15LH - 20LH \cdot (HR_0/HR_c) + 23. \quad (3)'$$

Each dependent variable affected the objective variable independently (partial correlation coefficients between the objective variable and each dependent variable: 0.89, 0.53, -0.48, 0.22, $p < 0.001$).

Equation (2)' is as follows:

$$\Delta SBP = SBP_c(1 - 15LH/SBP_c)(1 - 0.85HR_0/HR_c) + \varepsilon. \quad (2)'$$

Fig. 3. Correlations between SBP_0 and estimated SBP_0 and between DBP_0 and estimated DBP_0 . SBP_0 , base systolic blood pressure (BP); estimated SBP (SBP_0'), $SBP_0' = 0.85SBP_c \cdot (HR_0/HR_c) + 15LH - 20LH \cdot (HR_0/HR_c) + 23$; DBP_0 , base diastolic BP; estimated DBP_0 (DBP_0'), $DBP_0' = 0.9DBP_c \cdot (HR_0/HR_c) + 12LH - 16LH \cdot (HR_0/HR_c) - 44DBP_c/SBP_c + 35$; SBP_c , DBP_c , HR_0 , HR_c and LH are as in Fig. 2; x , values of x -axis; y , values of y -axis; $\bar{x} - \bar{y}$, mean of difference between x and y values.

The value of ε was $7.3LH \cdot HR_0/HR_c - 23$, and its mean $\pm$ SD were -9 ± 4.3 mmHg. This is an absolute value with relatively small scattering.

The equation for estimating DBP_0' is as follows (to minimize the margin of error in item ε , we employed DBP_c/SBP_c):

$$DBP_0' = 0.9DBP_c \cdot (HR_0/HR_c) + 12LH - 16LH \cdot (HR_0/HR_c) - 44DBP_c/SBP_c + 35. \quad (4)'$$

The coefficient of correlation of estimated base SBP or SBP_0' (x) with actual SBP_0 (y) was $r = 0.92$ ($y = x - 0.66$), with a mean error ($\bar{x} - \bar{y}$) of 0.82 ± 5.9 mmHg. The coefficient of correlation between estimated DBP or DBP_0' (x) and DBP_0 (y) was $r = 0.85$ ($y = x - 0.9$), with a mean error of 0.42 ± 5.5 mmHg (Fig. 3).

For each hypertensive group (WCH, WHO-I and WHO-II group) we examined the relations between estimated mean BP_0 (MBP_0) derived from SBP_0' , DBP_0' and clinic mean BP (MBP) derived from SBP_c and DBP_c ($MBP = \text{diastolic BP plus one-third of the pulse pressure}$) (Fig. 4). In terms of clinic

Fig. 4. Relations between clinic (casual) mean blood pressure (MBP_c) and estimated MBP_0 (base MBP) and between clinic (casual) HR (HR_c) and LF/HF . WCH, white-coat hypertensives ($\circ$); WHO-I, WHO stage I hypertensives ($\bullet$); WHO-II, WHO stage II hypertensives ($\triangle$); LF/HF , ratio of low frequency component (LF)/high frequency component of ECG-RR variability (HF).

MBP , it was hard to differentiate between WCH and the sustained hypertensive (WHO-I and WHO-II) group (predictive accuracy 65%). In terms of estimated MBP_0 , the predictive accuracy for discrimination (with the $D_{1,2}$ -function) was 88% (Fig. 4).

In Eqs. (3') and (4'), the need for the HR_0 value led us to consider a method of judging WHO-I and WCH without HR_0 . We examined the distribution chart (scatter plot) for each subject in the WCH and WHO-I groups. In the scatter plots, the clinic HR (HR_c) values were the horizontal axis and the LH values were the vertical axis (Fig. 4). Examination showed that in the WCH-group, LH values corresponding to HR_c values were lower than in the WHO-I group. Working out the

differential function ($D_{1,2}$) for both groups gave the discriminant-equation: $D_{1,2} = 0.123HR_c - 1.91LH - 5.27$ ($LH = 0.064HR_c - 2.76$, if $D_{1,2} = 0$). The differential predictive accuracy for the WCH-group and the WHO-I group was 82%.

Discussion

In the course of a single day, each individual experiences about 100,000 BP values (BP_i , $i=1, 2, \dots, 100 \times 10^3$) when measured directly (10, 13). The great influence of daily mental and physical activities exerted on these values means that they have poor reproducibility. Therefore, ambulatory BP monitoring (29, 30) or home BP measurement (31–33) has been used recently in ordinary clinics and many studies. Base BP (BP_0 , $i=0$), on the other hand, is the minimum value occurring at night during sleep, and has slight day-to-day fluctuation (2.4 ± 1.8 mmHg for MBP) (10). Because its reproducibility is high, base BP is a suitable index for BP evaluation (10–13). Individual values for a day's BP_i can be expressed by the equation (10) $BP_i = BP_0 \times \phi_i$ (ϕ_i = increment ratio) or the equation (12) $BP_i = BP_0 + \Delta BP_i$ ($\Delta BP_i = BP_0(\phi_i - 1)$ = pressure increment).

BP_0 is the true basal BP proposed by Smirk (9), which we adopted for the ambulatory BP monitoring method. Regulated mainly by total peripheral vascular resistance (21), BP_0 has a stronger correlation with left ventricular mass index than mean daytime BP_i and is more closely related to the severity of hypertension-related organ damage (10–13). Thus, base BP (basal BP or night BP) is useful from many standpoints, since it has 1) physiological meaning (10–13) (all BP_i values of an individual can be expressed as $BP_i = \text{base BP} + \Delta BP_i$, $i=1, 2, \dots, 100 \times 10^3$), 2) slight day-to-day fluctuation (10) (high reproducibility), and 3) stronger correlation with severity of hypertension (10–13) and prognosis (mortality) (9, 14) than daytime BP.

The pressure increment (ΔBP_i), however, is closely related to increases in cardiac output and heart rate, SNA (plasma norepinephrine concentration), LH, and baroreflex sensitivity (12, 21–23).

Many other researchers have reported the poor prognosis of patients whose nighttime BP is high (14) and the large number of patients with severe hypertension among individuals whose nighttime BP drops only slightly—*i.e.*, the non-dipper type (6). Non-dippers are defined as patients whose base BP is high and ΔBP_i slight.

Although there are various definitions (15–19) of the white-coat effect, white-coat hypertension occurred in subjects whose base BP was low and whose ΔBP_c ($i=c$; c , time at clinic) was high in this study. The white-coat phenomenon has been reported to affect 10–30% (21.5% in this study) of patients judged to have hypertension in outpatient clinics (1, 34–37). Measuring clinic BP alone, it is impossible to discriminate between WCH and mild hypertension (Fig. 4). It is therefore important to diagnose WCH for selecting antihypertensive medication in the outpatient clinic. Though it can be

diagnosed when BP is measured in the home or by the ambulatory BP monitoring method, WCH should be preferably evaluated in the outpatient clinic.

The present study analyzed the physiological factors in the difference between clinic BP and base BP (ΔBP_c) and considered methods of evaluating it simply in outpatients. A great deal of research has been devoted to investigating why WCH patients experience the white-coat effect (20, 24, 34–42), which involves increased ΔBP_c . Grassi (24) argued that the white-coat effect causes increased BP and HR as an alerting reaction and reported that microneurography reveals increased skin SNA and decreased muscle SNA. According to this line of thought, the white-coat effect is thus a reaction causing muscle vasodilation as a defense mechanism. It has also been suggested that in reaction to rising BP, baroreceptor stimulation may inhibit muscle SNA. The white-coat effect has also been ascribed to epinephrine, because its increase during emotional response dilates skeletal muscle vessels through stimulation of β -adrenergic receptors (43).

Pierdomenico *et al.* (39) reported that, in sustained hypertension, the kind of sympathetic hyperactivity seen in LH increases. This does not occur in instances of white-coat hypertension. As a result of microneurographical observations, Smith *et al.* (40) reported that the absolute values of muscle SNA are higher in WCH subjects than in normal subjects but lower than those in sustained hypertensive subjects, whereas baroreceptor reflex sensitivity remains about the same in WCH and normal subjects.

Our study was able to estimate ΔSBP —the difference between base SBP and clinic SBP—with the equation $(SBP_c - 15LH)(1 - 0.85HR_c/HR_0) + \varepsilon$ (coefficient of correlation between the true ΔSBP and inferred ΔSBP : $r=0.92$). Moreover, performing linear multivariate analysis again, based on substitution of SBP_0 for the relation to SBP_c , resulted in the equation $\Delta SBP = (SBP_0 - 28LH)(0.9HR_c/HR_0 - 1) + \varepsilon$ ($\varepsilon = 0.165LH \cdot HR_c/HR_0 + 6 < 10$ mmHg) (correlation coefficient $r=0.90$ between actually measured ΔSBP and inferred ΔSBP). Thinking in terms of these equations suggests the possibility that, in ΔSBP , HR_c/HR_0 provides positive feedback, whereas LH, which is an index of SNA, operates as a negative feedback loop. In other words, in the WCH group, the alert reaction causes large rises in SBP_c and HR_c , and the LH reaction is nearly the same as that in normotensive subjects (normal negative feedback by baroreceptor control) (Table 2). In the WHO-I group, on the other hand, the LH reaction is large, and baroreflex-caused inhibition of LH (SNA) may be slight. Thus, in the WCH-group, baroreceptor-heart-rate control (BRS) is maintained at nearly normal levels (35), and increases in LH in relation to ΔSBP are slight (34), but in the WHO-I group, it is possible that BRS drops, LH inhibition is slight, and LH rises (Fig. 4).

In the present study, direct measurements of BRS and SNA were not investigated. Cardiac BRS is different from muscle SNA-BRS (44). It remains uncertain which of these baroreceptor controls LH is related to cardiac BRS or SNA-BRS.

Further, our study has certain limitations. For example, because of the small number of subjects in the WCH-group, we did not investigate whether our theoretical equation applies to other WCH cases. Moreover, we are aware of the need to obtain HR_0 in the inference of SBP_0 and DBP_0 . Nonetheless, we believe that the basis of our theoretical equation is supported by reports on the correlation between spectral components of the variability of HR and muscle SNA (45) and the result of the inhibition of muscle SNA caused by the white-coat effect (24). In addition, as we have already reported (10, 46), estimating base BP makes it possible to judge the severity of hypertension.

Since the use of an HR recorder (27) (wristwatch type) permits easy measurement of HR_0 in the outpatient clinic, using Eqs. (3)' and (4)' makes it possible to estimate $\Delta BP_c (=BP_c - BP_0)$. Consequently, the new ΔBP -estimation device (BP-ECG monitor) enables us to infer true base BP (BP_0) in the outpatient clinic and is therefore useful in estimating the difference between BP_c and base BP (ΔBP_c), and also in predicting white-coat hypertension.

Acknowledgements

The authors wish to thank Shigehiro Ishizuka, Research and Development Section, A&D Co., Ltd., for creating and providing the BP-ECG monitor for estimating base BP and white-coat hypertension.

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