Abstract—The purpose of this study was to calculate statistically the minimum (base) blood pressure (BP) of nighttime (sleep-time) BP values obtained by ambulatory BP monitoring (ABPM) and to investigate its clinical significance. Twenty-four-hour recording of ECG with ABPM was performed directly (n=89) or indirectly (n=117) in 206 patients with essential hypertension. A telemeter was used for the direct method and a multi-biomedical recorder (TM2425) was used for indirect measurement. First, minimum heart rate (HR0=60/RR0) was determined from sleep-time ECG. The mean product of sleep-time diastolic BP (DBP) and pulse interval (RR) was divided by RR0 to obtain DBP0 [DBP0=(DBP×RR)/RR0]. The correlation between systolic BP (SBP) and DBP was used to determine SBP0 corresponding to DBP0. Statistical base mean BP (MBP0) was calculated from these values, and its reproducibility and relation to hypertension severity were investigated. MBP0 values were similar to true base values of sleep-time MBP obtained by the direct method (mean±SD difference, 2.0±2.4 mm Hg). Direct MBP0 criteria predicted hypertension severity (mild, moderate, or severe target organ damage) more accurately (predictive accuracy, 89%) than daytime MBP criteria (53%, P<0.01). Almost the same results were obtained using indirect MBP0 criteria. Day-to-day indirect MBP0 variation (mean absolute difference) was smaller (2.4±1.8 mm Hg) than day-to-day daytime and nighttime MBP variation (6.3±5.3 and 5.4±3.4 mm Hg, respectively; n=61, P<0.01), and the correlation coefficient between day-to-day variations of daytime MBP and physical activity (measured by an acceleration sensor) was 0.38 (P<0.05). In conclusion, statistical base BP was almost equal to true base (minimum) BP of sleep-time BP distribution. It was closely related to the severity of hypertensive organ damage, was highly reproducible, and is considered likely to serve stochastically and physiologically as a representative BP value in an individual subject. (Hypertension. 1998;32:430-436.)

Key Words: blood pressure monitoring, ambulatory ■ sleep ■ hypertension, essential

Statistical Base Value of 24-Hour Blood Pressure Distribution in Patients With Essential Hypertension

Osamu Tochikubo, Satoshi Hishiki, Eiji Miyajima, Masao Ishii

The enormous fluctuations occurring in blood pressure (BP) over a 24-hour period can involve as many as 100 000 directly measured intra-arterial BP values and ~100 measurements made indirectly by ambulatory BP monitoring (ABPM). A rational statistical way of treating these large numbers of values is fundamental to BP evaluation. Stochastically, each office BP or indirect ABPM value is only a sample of the 24-hour direct BP values occurring in an individual subject. Consequently, determining which of the measurement values to adopt as a representative BP value for an individual subject requires examination of the extent to which each value fulfills the following essential conditions.

First, the value must be logically sound, stochastically as well as physiologically. This means it must be a statistical parameter with a physiological basis. Second, to be clinically useful and applicable, it must be closely related to hypertension severity (organ damage). Third, it must be able to be measured noninvasively in clinical practice. Fourth, its measurement values must be highly reproducible and must demonstrate only slight day-to-day variation. Fifth, ideally, it should evaluate the prognosis and risk of hypertensive vascular complications.

Sir F. Horace Smirk1 reported that basal BP is more intimately related to hypertension severity than casual BP. Applying the same line of thought to 24-hour intra-arterial BP values, we reported base BP (that is, minimum BP occurring during nighttime sleep) to be a physiologically and stochastically important BP value.2-7 However, because base BP can be measured only with a large number of samples by the direct method, we found it necessary to devise a method of calculating statistical base BP with a small number of samples obtained indirectly by means of ABPM, and we have investigated the extent to which values obtained in this way satisfy the first 4 of the conditions set forth above.

Methods

Patient Groups

This investigation was carried out in 206 patients (107 men and 99 women between 30 and 74 years of age) with hypertension (office systolic BP [SBP] >140 mm Hg and diastolic BP [DBP] >90 mm Hg on at least 3 visits) who were taking no medication or for whom medication had been withdrawn at least 2 weeks previously. These patients satisfied the following inclusion criteria: no...
valvular defect, myocardial infarction, or secondary cause of hypertension. They were subdivided into 3 groups (Table 1). Group 1 (mild group with World Health Organization [WHO] stage I) consisted of subjects with no objective signs of hypertensive organic change. The their chest x-rays showed a cardiothoracic ratio (CTR) of <50%. The sum of SV1 and RV5, on their ECG was <4.0 mV, the echocardiographic left ventricular mass (LVM) index was <134 g/m² for male subjects or 110 g/m² for female subjects, and their Keith-Wagner-Barker (KW) ophthalmic category was lower than grade 1. They demonstrated no cerebral or renal hypertensive complications (plasma creatinine level was <91.5 μmol/L). Group 3 (severe group) consisted of patients with accelerated hypertension whose KW ophthalmic category was grade 3 or whose plasma creatinine level was >152 μmol/L. Group 2 (WHO stage II) was intermediate between these 2 (moderate group with LV hypertrophy and without retinopathy, plasma creatinine <152 μmol/L). Table 1 shows numbers of subjects and gender, age, mean office BP, and main clinical characteristics for each group.

Methods consisted of direct and indirect ABPM measurements. Direct measurements were made in 89 patients (47 men and 42 women; 37 from group 1, 38 from group 2, and 14 from group 3) after hospitalization. Indirect BP measurements were made in 117 patients (60 men and 57 women; 52 from group 1, 52 from group 2, and 13 from group 3) at the outpatient clinic. All subjects gave informed consent to participation in the study, and the study protocol was approved by the ethics committee of the Yokohama City University Department of Internal Medicine.

**Direct BP Measurement**

Although it has been reported previously, we here briefly outline the procedure whereby direct BP measurements were made. Using a system developed in our laboratory, we used the telemetric method to perform continuous 24-hour monitoring of intra-arterial pressure and ECG under almost unrestricted conditions. With patients under the procedure whereby direct BP measurements were made. Using a digital converter was used to input BP and ECG waves into a computer at a sampling rate of 1 kHz for subsequent computer processing to determine beat-to-beat heart rate (HR), SBP, and DBP.

In accordance with the hospital schedule, sleep-time (nighttime) was defined as the hours between 9 PM and 6 AM. The remainder of the 24-hour period was regarded as waking time (daytime). The 24-hour trendgrams and sleep-time frequency histograms of BP and HR were made by computer (Figure 1A and 1B).

**Measurement of True Base BP Values From Direct Recordings**

The minimum values (values corresponding to the 0.5% lower probability integral during 1 hour) of intra-arterial SBP and DBP were almost the same as baseline values during sleep-time (Figure 1A). Sleep-time frequency distributions for intra-arterial SBP, DBP, and HR were compiled; values corresponding to the 0.5% lower probability integral were taken as true base SBP and DBP.

**Measurement of Estimated Base BP Values From Direct Recordings**

Because true base BP values can be calculated only on the basis of large numbers of directly obtained samples (about 30,000 samples), we devised a new method for determining statistical (estimated) base BP values from a small number of either directly or indirectly obtained samples. HR can be measured noninvasively by ECG, which makes it possible to derive the minimum value (lowest 1% value; HRₜ) from the HR frequency histogram obtained during sleep-time. This determines the corresponding pulse interval (RR) or RRₜ (RRₜ=60/HRₜ is the lowest 1% value of HR histogram during sleep-time) (Figure 2). Base value DBPₓRR (product of DBP and RR) was almost equal to mean sleep-time DBPₓRR and mean waking-time DBPₓRR. Using this value, we calculated the mean of DBPₓRR during sleep-time: (DBPₓRR). Then, dividing this by RRₜ, we obtained the statistical base DBP (DBPₛ):  

\[
DBPₛ = \frac{(DBPₓRR)}{RRₜ}
\]

Because of the high positive coefficient of correlation (r) between direct SBP and DBP (r=0.70 to 0.98), we used the linear-regression formula \(SBPₚ=a×DBPₚ+b\) (where a is the regression coefficient and b is constant value) with sleep-time values to obtain the statistical base SBP (SBPₛ) corresponding to DBPₛ:  

\[
SBPₚ = a×DBPₚ+b
\]
both directly and indirectly (Figure 2A and 2B). In this study, its accuracy was evaluated first using directly obtained BP values and then with indirect BP measurements.

**Indirect BP Measurement**

The portable multi-biomedical recorder (TM2425, A&D Co Ltd) can simultaneously record 24-hour indirect BP and ECG and measure body position, motion (acceleration), and temperature. The BP accuracy of TM2425 was validated according to and satisfied the criteria of the Association for the Advancement of Medical Instrumentation. Body motion (activity) was measured by an acceleration pickup sensor, and cumulative values for 1 minute were recorded at 18-millisecond intervals at frequencies ranging from 1 to 10 Hz in the vertical direction, with a sensitivity of $4.1 \times 10^{-3}$ m/s². SBP and DBP were recorded at 30-minute intervals, and HRs were recorded beat-to-beat on ECG by TM2425. The process of obtaining indirect statistical base BP by computer is as follows (Figure 2B). First, a sleep-time HR distribution was compiled from the ECG obtained with TM2425. Arrhythmic beats were automatically excluded. HR frequency distribution, mean, SD, skewness (sk), and minimum (lowest 1%) value were calculated by computer, and HR₀ and RR₀ (60/HR₀) were derived. After indirect DBP₀ was obtained by means of Equation 1, Equation 2 was used to arrive at indirect SBP₀ (Figure 2B). The coefficient of correlation ($r$) between sleep-time SBP and DBP was often smaller than the corresponding value obtained with the direct method, but Equation 2 was applied only when $r \geq 0.6$ (n = 82). In instances in which $r < 0.6$ (n = 35), the following equations (arrived at stochastically from least-squares linear regression analysis performed on 82 patients in whom correlation between SBP and DBP was $r \geq 0.6$) were used for estimating SBP₀: $SBP₀ = DBP₀ \times [(SBP/DBP) + 0.05]$ and $(SBP/DBP) = mean SBP/DBP ratio during sleep-time. The difference between SBP₀ derived from these equations and SBP₀ derived from Equation 2 was 1.5 ± 4.9 mm Hg in the 82 patients. The indirect measurements were performed during the subjects’ daily routines, and sleep-times were determined from their diaries.
Echocardiographic Measurements

Because LV hypertrophy is related to hypertension severity, echocardiography was used to examine LVM. All subjects underwent standard M-mode and 2-dimensional echocardiography performed by a cardiologist using an echocardiograph equipped with a 2.5-MHz and a 3.6-MHz imaging transducer (SONOS 2500 ultrasound system, Hewlett-Packard Co). As recommended by the American Society of Echocardiography,14 LV dimensions were derived from 2-dimensionally guided M-mode tracings. LVM was calculated using the Penn convention15 and adjusted for body surface area (LVM index). Echocardiograms were read in a blinded fashion without knowledge of other findings.

Statistical Analysis

Standard statistical methods, including paired 2-sample t test, nonpaired t test, F test, χ2 test, sensitivity test, specificity test,16 and ANOVA were used. Least-squares linear regression analysis and Bland-Altman plotting method were performed for 2 variables. MBP criteria were determined by discriminant analysis17 to discriminate well between the groups (discriminant functions: Z12 = a1MBP + b12, Z23 = a2MBP + b23; Z12 (a12 and b12) and Z23 (a23 and b23) were determined to allocate a patient to group 2 if Z12 > 0 and to group 3 if Z23 > 0). Predictive accuracy was calculated as follows: (n1 + n2 + n3)/total number; n1, n2, and n3 were numbers of patients classified accurately into each group (1, 2, and 3) by MBP criteria. Values were expressed as mean±SD, and values of P<0.05 were considered significant. The Multiple Statistical Analysis Program (Social Survey Research Information Co, Ltd) was used for calculations.

Results

Comparison Between True Base BP and Statistical Base BP From Direct Recordings

The correlation between the true base DBP and statistical base DBP (direct DBP0) by the direct method was high (r=0.93). The mean difference between them was 2.6±4.8 mm Hg. A high coefficient of correlation (r=0.93) was also found between the true base SBP and statistical base SBP (direct SBP0). The difference between them was 1.0±6.0 mm Hg. MBP calculated from direct DBP0 and SBP0 was taken as direct MBP0. The difference between true base MBP and direct MBP0 assessed by paired t test and Bland-Altman plotting was not significant, although MBP0 tended to be higher than true base MBP (mean difference, 2.0±4.2 mm Hg) (Figure 4).

Statistical Base BP and Hypertensive Target Organ Damage

Waking-time mean MBP was obtained and designated MBPw. Investigation was then performed to determine whether statistical base MBP or MBPw is more closely related to hypertension (organ damage) severity (Figure 5, Table 2). MBP criteria (MBPw=110 to 129 mm Hg; MBP0=89 to 109 mm Hg) were established to discriminate well between the groups by discriminant analysis (Table 2).

Sensitivity and specificity for direct MBP0 criteria were almost equal to or higher than those for direct MBPw criteria (Figure 5, Table 2). The predictive accuracy (sum of accurately classified number/total number×100) of direct MBP0 criteria (79/89×100=89%) was significantly higher than that of direct MBPw criteria (47/89×100=53%). These results suggest that direct MBP0 criteria predict hypertension (target organ) severity more precisely than direct MBPw criteria.

In this case, MBPw is expressed as a function of φ×MBP0 (φ=MBPw/MBP0),5 and it becomes essential to know whether φ is independently related to hypertension severity. The absence of a significant difference in φ values among the 3 groups (Figure 5) indicates that φ contains no information related to hypertension severity. A negative coefficient of correlation (r=−0.43, P<0.01) was observed between direct MBP, and φ (Figure 5, bottom).

Almost the same results were obtained from indirect measurements (Figure 6, Table 2). There was a high correlation between indirect MBPw and echocardiographic LVM index (r=0.75, P<0.01; Figure 6). The correlation coefficient (r) between indirect MBP0 and indirect MBPw was 0.72, and r between indirect MBPw and LVM index was 0.61.

Mean physical activity (acceleration) during waking hours (ACTw) in group 3 patients was less than in groups 2 and
Day-to-Day Variation of Statistical Base BP

To investigate the reproducibility, we used a multi-biomedical recorder (TM2425) to observe daily (day-to-day) variation (mean absolute difference between values obtained in 2 measurements) in indirect MBP_0 and MBP_W (Figure 7). Day-to-day indirect MBP_0 variation was significantly less (2.4 ± 1.8 mm Hg) than daily indirect MBP_W variation (6.3 ± 5.3 mm Hg, P < 0.01). Furthermore, day-to-day indirect MBP_0 variation was significantly less than daily nighttime indirect MBP variation (5.4 ± 3.4 mm Hg, P < 0.01).

There was a significant correlation (r = 0.38, P < 0.05) between day-to-day MBP_W variation (first-day MBP_W vs second-day MBP_W) and physical activity variation (first-day ACT_w vs second-day ACT_w, where ACT_w is mean acceleration during waking hours).

### TABLE 2. Relationship Between MBP Criteria and Classified Groups According to Degree of Hypertensive Organ Damage

<table>
<thead>
<tr>
<th>MBP Criteria, mm Hg</th>
<th>No. of Patients, Direct Method (Indirect Method)</th>
<th>%, Direct Method (Indirect Method)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
</tr>
<tr>
<td>MBPW*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80–109</td>
<td>19 (30)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>110–129</td>
<td>16 (20)</td>
<td>15 (31)</td>
</tr>
<tr>
<td>130–185</td>
<td>2 (2)</td>
<td>22 (12)</td>
</tr>
<tr>
<td>Total</td>
<td>37 (52)</td>
<td>38 (52)</td>
</tr>
<tr>
<td>MBP0†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–89</td>
<td>33 (48)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>90–109</td>
<td>4 (4)</td>
<td>33 (46)</td>
</tr>
<tr>
<td>110–140</td>
<td>0 (0)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Total</td>
<td>37 (52)</td>
<td>38 (52)</td>
</tr>
</tbody>
</table>

*MBPW discriminant functions (Z_W = –0.076 MBPW + 8.4, when Z_W = 0, MBPW = 110 mm Hg; Z_W = –0.082 MBPW + 10.9 mm Hg, when Z_W = 0, MBPW = 129 mm Hg); †MBP0 discriminant functions (Z_0 = –0.15 MBP0 + 13.4, when Z_0 = 0, MBP0 = 89 mm Hg; Z_0 = –0.26 MBP0 + 28.4, when Z_0 = 0, MBP0 = 109 mm Hg).†P<0.05; ‡P<0.01 vs MBPW criteria.
Discussion

Because of the great influence of daily activity and duration of sleep, the mean of nighttime BP values and the day-night differences demonstrate low reproducibility. To compensate for this fault, we propose statistical base BP as a new index representative of nocturnal sleep-time BP. This study investigates the extent to which this new index serves as an individual representative BP value satisfying the conditions set forth in the introduction.

Sir F.H. Smirk first stated that for purposes such as measuring basal metabolism, basal BP was more closely related to hypertensive severity and mortality than casual BP, but supplemental BP (casual BP minus basal BP) was not related to them. Applying this concept to ABPM measured but supplemental BP (casual BP minus basal BP) was not related to hypertensive severity and mortality than casual BP, measuring basal metabolism, basal BP was more closely set forth in the introduction. 

Indirect MBP \( \text{MBP}_0 \) values demonstrated less day-to-day variation than the indirect MBP \( \text{MBP}_0 \) \( (\phi \times \text{MBP}_0) \) and nighttime mean MBP values (Figure 7). This means that daily activities and sleep duration may exert no influence on statistical base BP. It is therefore more logical to use it instead of mean nighttime BP as a value representative of sleep-time BP.

The circadian change in BP in human subjects is well recognized, with BP levels being lower at night, and this observation has led to the perception of hypertensive subjects as dippers (with a nocturnal BP fall or dip) and nondippers. There are many reports that nighttime BP is closely related to end-organ damage, which is more severe in nondippers than dippers. However, the reproducibility of BP dipping (nighttime BP/daytime BP) is poor. We suggest that the statistical base BP, instead of mean nighttime BP, may be useful for evaluating the extent of the dipping phenomenon (dipping corresponds to \( \phi \) value).

It is true that we should compare indirectly measured statistical base BP with true base BP obtained by means of the direct method, but such an investigation would be very difficult because of the great burden imposed on subjects by the need for simultaneous 24-hour measurement of both direct and indirect BP. In addition, there are ethical reasons for rejecting such a practice. Our inability to perform this kind of study prevents our being able to conclude yet whether statistical indirectly measured base BP is consistent with true base BP value obtained with the direct method.

Nonetheless, statistical base BP is considered significant as a BP value that can serve as a normalized BP value free of the

**Figure 7.** Scatterplot shows differences in MBP between the first and second days. Indirect MBP \( \text{MBP}_0 \) indicates indirect statistical base MBP; indirect MBP \( \text{MBP}_w \), mean of indirect MBP during waking time; \( |y_2 - y_1| \), mean absolute difference between indirect MBP \( \text{MBP}_w \) on first day and indirect MBP \( \text{MBP}_w \) on second day; \( |x_2 - x_1| \), mean absolute difference between indirect MBP \( \text{MBP}_0 \) on first day and indirect MBP \( \text{MBP}_0 \) on second day; \( \circ \), MBP values on first day or second day in group 1; \( \triangle \), MBP values in group 2; and \( \odot \), MBP values in group 3.
effects of environmental conditions. It reflects true basal BP, and because it approximately fulfills the first 4 of the 5 conditions set forth above (logical, clinical, noninvasive, and highly reproducible conditions), statistical base BP is believed to be suitable as an individual representative BP value. Determination of its relation to the second and fifth conditions (indicating severity and prognosis of hypertension) requires further study involving noninvasive BP measurement in a much larger number of subjects. The present study is only the first step toward achieving this ultimate goal.

Acknowledgments

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