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

Osamu Tochikubo, Satoshi Hishiki, Eiji Miyajima, Masao Ishii

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±4.2 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

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.2-3 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...

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TABLE 1. Main Clinical Characteristics of 3 Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (WHO Stage I)</th>
<th>Group 2 (WHO Stage II)</th>
<th>Group 3 (Accelerated Hypertension)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (M/F)</td>
<td>89 (44/45)</td>
<td>90 (46/44)</td>
<td>27 (17/10)</td>
</tr>
<tr>
<td>Age, y</td>
<td>42±13</td>
<td>48±11</td>
<td>43±8</td>
</tr>
<tr>
<td>KW classification, grade</td>
<td>0–1</td>
<td>1–2</td>
<td>3</td>
</tr>
<tr>
<td>CTR on chest x-ray, %</td>
<td>44±3</td>
<td>53±3</td>
<td>55±4</td>
</tr>
<tr>
<td>SV1+RV5 (ECG), mV</td>
<td>3.6±0.4</td>
<td>4.3±1.2</td>
<td>5.7±1.0</td>
</tr>
<tr>
<td>LVM index, g/m²</td>
<td>104±16</td>
<td>151±22</td>
<td>205±37</td>
</tr>
<tr>
<td>Plasma creatinine, μmol/L</td>
<td>77.7±9.1</td>
<td>85.4±11.4</td>
<td>173±10.6</td>
</tr>
<tr>
<td>Office BP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>162±9.5</td>
<td>179±16.0</td>
<td>217±23.6</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>99±4.9</td>
<td>105±4.8</td>
<td>128±4.8</td>
</tr>
</tbody>
</table>

Values are mean±SD. KW indicates Keith-Wagner grade: 0–1=normal or slightly narrowed retinal arteri,

valvular defect, myocardial infarction, or secondary cause of hyper- tension. 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.6 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).

Next, statistical base mean BP (MBP0) was calculated from DBP0. This method for obtaining statistical base BP values is applicable to BP values obtained 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 (nightime) 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 (Figure 1B).

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) from HR histogram during sleep-time. The minimum values (values corresponding to the lowest 1% value of HR histogram during sleep-time) were almost equal to mean sleep-time DBP×RR and mean waking-time DBP×RR. Using this value, we calculated the mean of DBP×RR during sleep-time: (DBP×RR)s. Then, dividing this by RR0, we obtained the statistical base DBP (DBP0):

(DBP0) = (DBP×RR)s/RR0

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 SBP=a×DBP+b (where a is the regression coefficient and b is constant value) with sleep-time values to obtain the statistical base SBP (SBP0) corresponding to DBP0:

(SBP0) = a×DBP0+b

Next, statistical base mean BP (MBP0) was calculated from DBP0 and SBP0, [MBP0=(SBP0−DBP0)/3+DBP0]. This method for obtaining statistical base BP values is applicable to BP values obtained...
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.\textsuperscript{12,13} 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/s\(^2\).\textsuperscript{12} 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.\textsuperscript{12} HR frequency distribution, mean, SD, skewness (sk), and minimum (lowest 1%) value were calculated by computer, and HR\(_0\) and RR\(_0\) (60/HR\(_0\)) were derived. After indirect DBP\(_0\) was obtained by means of Equation 1, Equation 2 was used to arrive at indirect SBP\(_0\) (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 \(r = 0.6\) were used for estimating SBP\(_0\): SBP\(_0\) = DBP\(_0\) \times \left(\frac{\text{SBP}}{\text{DBP}}\right)_{s} \times 1.05 + 42.1 = 112\) and (SBP/DBP)\(_s\) = mean SBP/DBP ratio during sleep-time. The difference between SBP\(_0\) derived from these equations and SBP\(_0\) derived from Equation 2 was 1.5\pm 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.
With the aim of investigating the reproducibility of statistical base BP, 24-hour measurements were performed twice (Figure 3) using TM2425 for 61 patients (31 men and 30 women). The second measurement was made more than 1 week after the first (median interval of 3 weeks; range, 1 week to 2 months).

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 (cutoff point) were determined by discriminant analysis17 to discriminate well between the groups (discriminant functions: Z₁₂=a₁MBP₁+b₁; Z₂₃=a₂MBP₂+b₂; Z₁₂ (a₁ and b₁) and Z₂₃ (a₂ and b₂) 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 MBP₀. Investigation was then performed to determine whether statistical base MBP or MBP₀ is more closely related to hypertension (organ damage) severity (Figure 5, Table 2). MBP criteria (MBP₀=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 MBP₀ 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 MBP₀ criteria (47/89×100=53%). These results suggest that direct MBP₀ criteria predict hypertension (target organ) severity more precisely than direct MBP₀ criteria.

In this case, MBP₀ is expressed as a function of ϕ×MBP₀ (ϕ=MBP₀/MBP₀),1 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 MBP₀ 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 MBP₀ and echocardiographic LVM index (r=0.75, P<0.01; Figure 6). The correlation coefficient (r) between indirect MBP₀ and indirect MBP₀ was 0.72, and r between indirect MBP₀ 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 1.
group 1 (8.4±2.4: 14.2±6.8: 18.7±6.4×10⁻³ m/s² per minute; P<0.05).

**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 MBP₀ and MBPₖ. Day-to-day indirect MBP₀ variation was significantly less (2.4±1.8 mm Hg) than daily indirect MBPₖ variation (6.3±5.3 mm Hg, P<0.001). Furthermore, day-to-day indirect MBP₀ 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 MBPₖ variation (first-day MBPₖ–second-day MBPₖ) and physical activity variation (first-day ACT₆–second-day ACT₆, where ACT₆ 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 (Z₁₂=−0.076 MBPW+8.4, when Z₁₂=0, MBPW=110 mm Hg; Z₁₂=−0.002 MBPW+10.9 mm Hg, when Z₁₂=0, MBPW=129 mm Hg); †MBP₀ discriminant functions (Z₁₂=−0.15 MBP₀+13.4, when Z₁₂=0, MBP₀=89 mm Hg; Z₁₂=−0.26 MBP₀+28.4, when Z₁₂=0, MBP₀=109 mm Hg). ‡P<0.05; §P<0.01 vs MBPW criteria.
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.

Individual representative BP value satisfying the conditions index representative of nocturnal sleep-time BP. This study sate for this fault, we propose statistical base BP as a new manifestation of sleep takes the most efficient pulse base MBP; indirect MBP W, mean of indirect MBP during waking time; $y_i - y_j$, mean absolute difference between indirect MBP W on first day and indirect MBP W on second day; $x_i - x_j$, mean absolute difference between indirect MBP W on first day and indirect MBP W on second day in group 1; MBP values on first day or second day in group 2; MBP values in group 3.

**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 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 values, we have specified minimum sleep-time BP (base BP) and have repeatedly studied its significance. Instead of manifesting a gaussian distribution, intra-arterial BP and HR values obtained during nighttime and daytime are distributed asymmetrically with a levopositional mode (mode $<$ mean) in a manner approximating a gamma distribution that has a minimum value (location parameter). We found that base BP was almost the same as the location (L) parameter of the BP frequency distribution, which approximated a gamma distribution. The L parameters took approximately the same values for both nocturnal sleep-time and waking-time BP distributions and seemed to be the starting point for their gamma distributions. True base BP corresponds to an actual measured value of the L parameter, which is an important parameter of these BP distributions.

BP reaches a minimum value during the electroencephalographic slow-wave phase. The base BP waveform manifesting itself at this time takes the most efficient pulse interval (RR) for producing a maximum per-minute waveform area, which indicates a maximum per-minute blood flow in relation to BP value. Moreover, at this time, base BP demonstrates a higher correlation with total peripheral vascular resistance and arterial elastic modulus than MBP W. DBP W and SBP W, which are statistical base BP values, are the estimated values for the true base BP values of each of their frequency distributions and are thought to satisfy the statistical and logical conditions set forth in the introduction.

Every BP, $(i=1 \cdots n)$ during daytime and nighttime may be expressed by the formula $BP_i = \phi_i \times$ base BP $(\phi_i =$ incremental ratio). The $\phi_i$ value, which can be analyzed by means of the formula $\phi_i = FI + BI$ (FI indicates cardiovascular function index; BI, baroreflex function index), may vary because of the changes of cardiovascular and baroreflex responses to physical and mental activity. Because $\phi (MBP_0 / MBP_1)$ is unrelated to hypertension (target organ) severity and $\phi$ correlates with physical activity (group 3 patients had lower $\phi$ and lower physical activity), using MBP W is considered more logical than using MBP 0 for evaluation of hypertension severity. Figure 3 shows typical variations of $\phi$ value and indirect MBP W caused by changes in physical activity (acceleration) monitored in 1 patient with TM2425. Although the means of waking-time BP and nighttime BP are also statistical parameters, because they are greatly influenced by daily activities, their $\phi$ values may be changed by alterations in such factors as external temperature, insufficient sleep, duration of sleep, physical activity (acceleration), emotional stress, and autonomic nervous activity.

Indirect MBP 0 values demonstrated less day-to-day variation than the indirect MBP W 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 new index 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
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.

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The authors wish to thank Shigehiro Ishizuka and Kenichirou Yasaka, Research and Development Section, A&D Co, Ltd, Tokyo, Japan, for providing the computer program used for statistical base BP calculations of TM2425 recordings. This program is commercially available.

References
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