RELATIONSHIP BETWEEN BLOOD PRESSURE AND HEART RATE WHILE AWAKE AND ASLEEP IN PATIENTS WITH MILD ESSENTIAL HYPERTENSION

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Blood pressure (BP) and heart rate (HR) (BP waveforms) are affected by external stress during waking and BP is reduced to its lowest level (base BP) during sleep. This study investigated the relationship between BP waveforms while awake and base BP waveforms during sleep. The intra-arterial BPs of 64 inpatients (34 males and 30 females, age: 42 ± 11, mean ± SD) with mild essential hypertension were measured for 24 h by the telemetry method. The average ln (SBP/DBP) (m) while awake and the m at base BP (In: natural logarithm, SBP: systolic BP, DBP: diastolic BP) had approximately the same values in each patient (mean difference: −0.02 ± 0.07). The product of the RR interval (60/HR) and DBP (RR × DBP) while awake and at base BP had almost the same value (mean difference: −3.2 ± 10 mmHg · sec). According to the Windkessel model, the RR interval during which blood-flow volume in relation to the m value is at its highest can be inferred as S (e^m−1)/(e^m−m−1) (S: systolic time). Using this formula, we developed a formula to estimate base RR from waking m, BP, and RR. Calculations with this estimate formula produced a very slight difference (0.0 ± 0.1 sec) between estimated and actual values for base RR. For the most part, it was possible to infer the base DBP value from the estimated base RR using RR × DBP while awake (mean difference: −3.7 ± 7.0 mmHg). These results suggest that the base BP waveform may be the most efficient pattern, and that waking BP waveforms change based on the base BP waveform during sleep.

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TWO-MONTH-FOUR-HOUR observations of intra-arterial blood pressure (BP) and heart rate (HR) reveal extremely large variations. However, in both normotensive subjects and mild hypertensive patients, both BP and HR are reduced to minimal and stable values (base line) during sleep (at the slow-wave stage on the electroencephalogram)1,2 We previously defined these values as base BP and base HR and reported on their significance1,2 Since base BP occurs during sleep, it can be used as a representative value for BP while asleep.

It is thought that base BP and base HR occur at those times of day when sympathetic nervous activity is at its lowest and when a minimum amount of stress is affecting the cardiovascular system2,3.

In evaluating an individual’s BP, it is important to analyze the diurnal BP variation

Key words:
- Windkessel model
- Diurnal blood-pressure variation
- Base blood pressure
- Base heart rate
and base BP, and to identify relationships between the two. A close relationship exists between changes in 24 h BP and HR, and a fixed mutual relationship exists between 24 h systolic BP (SBP) and diastolic BP (DBP). Employing the classic Windkessel model, this study investigated reciprocal relationships among 6 factors (SBP, DBP, and HR while awake, and base SBP, base DBP, and base HR during sleep) and attempted to determine the rules if any, which exist among them. In addition, since base BP must currently be measured directly during sleep, we examined the possibility of inferring base BP and base HR (or base RR=60/base HR) values from waking BP waveforms.

SUBJECTS AND METHODS

Estimation of Base HR (base RR)
To analyze 24 h BP waveforms, we employed the Windkessel model, according to which the volume of blood forced from the left ventricle into the aorta within the dt interval of the cardiac contraction (systolic) phase is taken to be Q·dt. If Q is the volume of blood ejected from the heart per dt, blood pressure within the aorta at time t is P, and total peripheral vascular resistance is R, then Q=\frac{P}{R}. If pressure gain within the aorta after time dt is dP, the increment in blood volume is dV, and the volume elastic modulus is E, then E=dP/dV.

Since \frac{dV}{dt}=Q\frac{dt}{dt}=Q\frac{dP}{dt}=\frac{1}{E} \frac{dp}{dt}, when Q(t)=P/R+1/E (dp/dt). If Q(t) is a square wave, then blood flow (Q)=Q_0 during the systolic phase (0≤t≤S, where S=systolic ejection time). It is assumed that during the diastolic phase (S≤t≤D) with Q=0, if we integrate the above formula under the initial conditions that t=0 and P=DBP (DBP: diastolic BP), then P=R \left\{Q_0(Q_0-DBP/R) e^{-E/R}(0≤t≤S)\right\}(e: exponential). However, if we integrate the same formula under the initial conditions that t=S and P=SBP (SBP: systolic BP), then P=SBP \times e^{-E/R/(s)}(S≤t≤S+D). In other words, during the diastolic phase, arterial BP (P) diminishes only by the coefficient e^{-A/(s)} (where A=E/R).

During the base-line period, the value D, which represents the period of cardiac dilation (diastolic time), is large. Moreover, we postulated a constant D value that would produce a maximum blood-flow volume for a constant S. In other words, this could be
considered the value for D at which peripheral blood flow per constant systolic time (S) is most efficiently ejected at base HR during sleep.

Since stroke volume (SV) = 1/R^2pdt, the larger the BP-wave integral value, the greater the volume of blood flow. If blood-flow volume for 1 min of the diastolic phase is taken to be Qd, then Qd = 60/(S + D)·(1/R)·∫SBP·e^−At dt and Qd = 60/(S + D)·SBP [1−e^−AD]/RA. [1−e^−AD]/A(S + D) represents the maximum value in relation to any given S value. If this maximum D value is at m = ln (SBP/DBP), then the value for A at this time is A = m/D. Consequently, D = mS/(e^m−m−1) may be derived (Fig.1 shows the value for maximum D when S=0.2 sec and m=0.5). Briefly, if m has a constant value for each individual, it may be assumed that, in the base HR, D is related only to the values m and S. In such a case, the RR interval at maximum D may be expressed as RR = S + D = S + mS/(e^m−m−1) = S(e^m−1)/(e^m−m−1). Since (e^m−1) = PP/DBP (where PP=SBP-DBP), it may also be expressed as RR = S/(1-DBP/PP×m).

Subjects
Outpatients who were not receiving treatment and who had DBP of more than 90 mmHg on 3 different days, were hospitalized. During hospitalization, they were kept on a diet limited to 7g of salt daily. Routine examinations showed that none of the patients had secondary hypertension. Subjects for the study included 64 patients (34 males and 30 females; ages 22–64) whose auscultatory DBP, after a week of hospitalization, remained at more than 90 mmHg. The mean age of the subjects was 42.3±10.8 (mean±SD). Their mean auscultatory SBP was 160±9.2 mmHg, and their mean auscultatory DBP was 98±4.1 mmHg. Their serum creatinine levels were below 1.3 mg/dl, and electrocardiograms (ECG) revealed no ischemic ST-T changes. None of the subjects had a history of myocardial infarction, angina pectoris, or cerebro-vascular disorder, and all were classifiable as mild or moderate essential hypertension. After a thorough explanation of the nature of direct 24 h BP recording, all of the patients gave their informed consent to the study.

24-hour Direct BP Measurement
After 7 to 10 days of hospitalization, 24 h direct BP measurement was performed in the following manner, as previously reported. According to the Seldinger method, a slender teflon cannula (Arrow International, Inc., F-035-5.G18) was inserted into the left brachial artery. The cannula and a BP transducer were connected by means of a low compliance, 30 cm extension tube (North American Instrument Co., High-frequency monitoring lines). The transducer (Statham model P50) was attached by means of adhesive plaster to the left thoracic wall at the height of the heart. A small, 4-channel transmitter (Nihon Denki Sanei Co. Led., Model 415) and a microinfusion pump, to prevent blood coagulation within the catheter, were attached at the waist. The subjects all awoke at 06:00 and went to bed at 21:00. Otherwise, they were at liberty to move about the hospital. The microinfusion pump, which was produced especially by our laboratory, measures 10×5×3 cm and weighs 250g. It is capable of injecting physiological saline solution containing 5 μ/ml of heparin into the catheter at a rate of 2 ml per hour. The transmitter transmits arterial BP, ECG, electroencephalograms and electro-oculograms. Throughout the 24 h period, transmitted signals were recorded by a recticorder (Nihon Denki, Sanei Rectigraph-8K) and a tape recorder (portable tape recorder R-260, TEAC Co.). Although the frequency characteristic of the BP transducer was about 100 Hz, when the catheter and the telemeter were included, the system had a frequency response flat to at least 25 Hz.

Data Analysis
Data on the tape recorder were computer-analyzed (NEC PC-9801). The R wave of the ECG was the trigger signal, and the maximum and minimum values in BP waveforms after the R wave were taken to represent SBP, and DBP, respectively. Instantaneous heart rate (HR = 60/RR-interval) was calculated from the RR interval. Input signals were sampled at a speed of 200 Hz/sec, and pressure calibrations were made by means of a sphygmomanometer before and after each measurement. Trendgrams and frequency histograms were compiled on the basis of beat-to-beat values recorded on floppy disks.
Relationship Between Blood Pressure and Heart Rate

Fig. 2. A trendgram of SBP and DBP values for 10 min periods during 24 h. The upper black dots are mean SBP/DBP values. The lower black dots constitute a time-lapse representation of the ratio of \([DBP \times RR/\text{Estimated (base RR)}]\) to estimated base DBP [Estimated (base RR)\(=S(e^m-1)/(e^m-1-m)\), SBP: systolic BP, DBP: diastolic BP].

\[
Y = 0.93X + 0.15 \quad (r=0.80) \\
X - Y = -0.04 \pm 0.11
\]

Fig. 3. Relationship between SBP/DBP while awake and SBP/DBP at base BP. The figure on the left shows the relationship between mean waking SBP/DBP values (X axis) values during sleep (Y axis) for each subject. The figure on the right shows similar information for \(\ln (\text{SBP/DBP})\); i.e., \(\ln \): natural logarithm.

Based on both BP waves recorded in the recticorder and computer data, SBP was determined to be from 30 to 300 mmHg and DBP occurred from 30 to 160 mmHg. Anything outside of these limits was considered noise. Frequency histograms were prepared for SBP, DBP, and HR for the period between 21:00 and 06:00. The 0.5% lower limits of the frequency histograms were defined as base SBP, base DBP and base HR\(^{1,2}\). Waking HR and BP values were averaged for the period from 06:00 to 21:00.

Correlation was determined by a linear regression analysis. The coefficients of \(a\) and \(b\) in \(Y = aX + b\) were also calculated. Multivariate linear regression analysis was em-
Fig. 4. Relationships between BP×RR while awake and BP×RR at base BP. The figure on the left shows relationships between mean waking SBP×RR values (X axis) and base SBP×RR values (Y axis) during sleep. The figure on the right shows similar information for DBP×RR (SBP=systolic BP, DBP=diastolic BP, RR=RR interval on ECG).

Fig. 5. Inferring base RR from waking BP waveforms and the formula: $S = \frac{e^m - 1}{(e^m - m - 1)}$. $S = 0.474 - 0.1 \times (3.1 - \sqrt{RR}) \times (DBP/PP)$; e is exponential, m is ln (SBP/DBP), $\sqrt{RR}$ is the square root of the mean waking RR, DBP is the mean waking diastolic BP, and PP is the mean waking pulse pressure (PP=SBP-DBP).

Employed for multiple data. Data are presented as the mean ± standard deviation (SD).

To compare two groups, paired t-tests were performed. A difference of $P<0.05$ was considered significant. In addition, mean $X-Y$ and their percentages 100 $(X-Y)/Y$ (%) were calculated for each X and Y.

RESULTS

Relationships Between SBP and DBP
Twenty-four-hour observations showed that SBP and DBP fluctuate in parallel. To simplify the observations, mean values for SBP/DBP ratios for each 10 min period were calculated for the entire 24 h (Fig. 2).

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SBP/DBP ratios fluctuated less than BP variations. For the sake of further simplification, we examined the correlation between mean waking SBP/DBP (X axis) and base SBP/DBP (Y axis) (Fig. 3). The coefficient of correlation (r) between the two was r=0.80. The value for X tended to be slightly smaller than that for Y (X−Y=−0.04±0.11, P<0.01), and the mean of 100 (X−Y)/Y was −2.4±7.0%.

The coefficient of correlation between the mean waking ln(SBP/DBP) (m) (X axis) and ln(SBP/DBP) base (Y axis) was 0.81. Although X was less than Y (the mean value of X−Y was −0.02±0.07, P<0.05), 100 (X−Y)/Y was −2.4±8%. If we can ignore
an error of this magnitude, then the values are almost the same (m-value constancy).

Relationship between BP and HR

Similarly, observations of fluctuations in BP and HR over a 24 h period revealed a parallel relation: i.e., when BP rose, HR also tended to rise. HR was converted into the RR interval (RR=60/HR). When the products of SBP and RR (mmHg·sec) were examined (Fig. 4), a strong correlation ($r=0.78$; $P<0.001$) was observed between SBP×RR while awake (SBP×DBP waking) and base SBP×RR (SBP×RR base during sleep). However, the mean difference in their absolute values ($X-Y$) was $-8.1 \pm 14.7$ mmHg·sec, and the mean 100 ($X-Y$)/Y value while awake was lower than that for the base value (difference: $-5.1 \pm 11.2\%$, $P<0.01$).

The coefficient of correlation between waking DBP×RR and base DBP×RR was $r=0.77$. The mean difference between the two ($X-Y$) was $-3.2 \pm 10.1$ mmHg·sec. The 100 ($X-Y$)/Y value while awake was on an average $-2.5 \pm 13\%$ lower than the base value, but this difference was not significant (DBP×RR constancy).

Inferring Base HR and Base DBP from Waking BP and HR

The equation for predicting base RR (60/base HR) is assumed to be $S (e^{m-1})/ (e^{n-1} - m)$, where $m=\ln(SBP/DBP)$ while awake. Performing multivariate analysis to adjust S to base RR gives $S=0.474-0.1 \times (3.1-\sqrt{RR})\times (DBP/PP)$ (where $\sqrt{RR}$ is the square root of the mean waking RR, DBP is the mean waking DBP, and PP is the waking pulse pressure). In attempting to infer base RR values (estimated base RR: X values) from S, it is necessary to examine the correlation between these values and actual base RR (Y values). Such an examination shows that $r=0.71$, $X-Y$ is $0.0 \pm 0.1$, and the mean error [100×($X-Y$)/Y] is $0 \pm 5.3\%$ (Fig. 5).

The estimated base HR was obtained from the mean SBP, DBP, and RR values for every 10 min interval for 24 h (Fig. 6).

By taking advantage of the constancy of SBP×RR and estimated base RR, it is possible to infer base SBP from waking BP waveforms [(SBP×RR) waking/(estimated base RR)]. An examination of the correlation between estimated base SBP and actual base SBP shows that $r=0.81$, with a mean difference of $-8.0 \pm 9.9$ mmHg (Fig. 7). The coefficient of correlation between base DBP and estimated base DBP [(DBP×RR) waking/(estimated base RR)] is $r=0.80$, with a mean difference of $-3.1 \pm 7.0$ mmHg. On the basis of the mean SBP, DBP, and RR values for each 10 min interval over a 24 h period, actual base DBP can be inferred from (DBP×RR) waking/(estimated base DBP).
Relationship Between Blood Pressure and Heart Rate

In other words, on the basis of waking BP waveforms \([m = \ln(SBP/DBP), DBP/PP\]
and \(RR\) values), it is possible to infer an approximate base \(RR\). Furthermore, because of the constancy of \(DBP \times RR\) these values can be used to provide a rough estimate of the base \(DBP\).

**DISCUSSION**

In this study we examined reciprocal relationships between waking BP waveforms (SBP, DBP, HR) while awake BP waveforms (base SBP, base DBP, base HR) while asleep.

The first characteristic we examined was the ratio of SBP to DBP (SBP/DBP). The mean waking value for this ratio was about 2.4% smaller than the mean value during sleep. In comparison with diurnal BP fluctuation, this difference was surprisingly small. SBP was expressed as the sum of pulse pressure (PP) and DBP (SBP = PP + DBP). Consequently, SBP/DBP = 1 + PP/DBP. PP magnitude is determined by the interaction between the incident-pressure wave generated by left ventricular ejection and one or more reflected waves generated by the arterial system. The magnitude of the incident wave depends on the wave developed by left ventricular ejection, arterial stiffness, and the attenuation characteristics of the vascular tree (wave reflection). Left ventricular ejection and arterial stiffness frequently increase when DBP rises. PP also tends to rise, although not always in a relationship of equilibrium. Furthermore, the PP of peripheral arteries is influenced by body position.

This explains why PP/DBP, and consequently SBP/DBP, is slightly smaller while awake than while asleep. A high degree correlation was observed between 24 h SBP and DBP in mild hypertensive patients (mean coefficient of correlation = 0.85 ± 0.07). This relationship can be approximately expressed by the linear regression formula \(SBP = a \times DBP + b\). If \(b\) is set close to zero, in order to modify this formula to \(SBP/DBP = a + b/DBP\), it should be possible to obtain a constant 24 h value. Actually, however, since \(b\) is not zero, the greater the DBP—or the higher the waking BP reading—the smaller \(a + b/DBP\) becomes. Still, if this small error can be considered negligible, then SBP/DBP is approximately the same while awake and while asleep. Therefore, in (SBP/DBP) (i.e., \(m\)) becomes virtually constant while both awake and asleep for each individual (\(m\)-value constancy).

We next examined \(DBP \times RR\) which was smaller while awake than while asleep by a mean of −3.2%. When large fluctuations in DBP and HR are taken into consideration, it seems that this value is a constant with physiological significance, rather than being merely accidental. On the other hand, SBP × RR was smaller while awake by a mean of −5.1%. Earlier research showed a significant correlation (\(r = 0.60 \pm 0.12\)) between DBP and HR in mild hypertensive patients; although baroreceptors play a role in this relationship. The regression equation \(DBP = aHR + b\) becomes \(DBP = 60a/RR + b\), and eventually \(DBP \times RR = 60a + b \times RR\). Foreseeably, \(b \times RR\) is small since the RR value is small while awake. However, because the value for \(b\) is close to zero, if a certain degree of error is overlooked, then the average \(DBP \times RR\) values while awake and while asleep are practically the same (constancy of \(DBP \times RR\)).

Since both SBP/DBP and DBP × RR while awake and while asleep were virtually constant, we investigated methods for inferring RR during sleep from the relationship between SBP/DBP and waking BP waveforms. Fundamentally, we assumed that waking BP waveforms contain information regarding BP during sleep, and that BP waves during sleep represent the state of maximum stability when external stress is slight. In the classical Windkessel model, the plane axis in the BP wave and the area surrounding the wave are proportional to stroke volume (SV) \([SV = \int_{0}^{\infty} P(t)dt/R, \text{where } R = \text{total peripheral vascular resistance}]\). Since the blood-flow volume (Qd) of the diastolic phase (diastolic time D) during 1 min can be expressed as \(Qd = 60(S + D) - SBP \cdot [1 - e^{-AD}]/RA\), it is conceivable that maximum blood-flow volume occurs at the most efficient value for \(D\); i.e., \((1 - e^{-AD})/(S + D)\). If \(m = \ln(SBP/DBP)\) is a constant value, then the value for \(D\) that produces the maximum value of Qd in relation to \(m\) is \(mS/(e^m - m - 1)\). In other words, the most effective value for \(D\) in relation to given values for \(m\) and \(S\) is \(mS/(e^m - m - 1)\) (Fig. 1.).
Since the value for S is uncertain, we obtained it by means of multivariate analysis of base RR and mean values for waking BP and RR. The formula $S = 0.472 - 0.1 \times (3.10 - \sqrt{RR})\times(DBP/PP)$ was derived from waking values. Calculating base RR from these $S$ and $m$ values led to the supposition of an error of $0.0 \pm 5.3$ sec. Fig. 6 gives base RR (here base HR) values inferred for each 10 min period from waking SBP, DBP, and RR. Similarly, it was possible to infer base DBP on the basis of both base RR (estimated base RR) and the constancy of $DBP \times RR$ (Fig. 2).

The formula $S (e^m-1)/(e^m-1)$ that we postulated for base RR lacks an adequate basis. For some subjects, we measured actual S values in waking BP waveforms and base BP waveforms, and used these values to calculate estimated RR [$=S(e^m-1)/(e^m-1)$] in order to determine relationships between estimated RR and true RR. This investigation was performed using sample values. In base BP, the similarity between estimated RR and true RR (60/HR) was great. However, in casual waking BP, this similarity was slight (Fig. 8). An examination of this situation on the basis of all S values for a 24 h period is now required. A computer program to perform this task is being developed.

Nevertheless, the limited results set forth above suggest that waking BP waves contain information regarding BP waves during sleep, and base BP waveforms during sleep represent the most efficient and maximum blood flow in relation to constant $m$ and S values. In other words, waking BP waveforms change on the basis BP waveforms during sleep.

**Study Limitations**

PP, DBP, and SBP/SBP are influenced by wave reflection. However, the Windkessel model does not consider the shape of the pressure wave reflected from the periphery. In this study, S was calculated by means of inductive statistics. In addition, since blood flow (Q) is not a square wave, our future task is to develop a more detailed theoretical formula and analyze relationships with actual BP waveforms.

**REFERENCES**


