Relationship between Circadian Variation of Ambulatory Blood Pressure and Age or Sex in Healthy Adults

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Twenty-four-hour ambulatory blood pressure (BP) was monitored in 540 healthy Japanese adults whose casual BP was less than 140 mmHg in systole and less than 90 mmHg in diastole. A total of 304 men and 236 women, ranging in age from 20 to 79 years, with a mean of 40.9 ± 12.8 years, were studied. BP was measured every 30 min using ABPM-630 (Nippon Colin Co.) for 24 h in 395 subjects and for 48 h in 145 subjects. Periodic regression curves were obtained and the coefficients of determination (R^2) was calculated for each periodic component. The periodic regression curves by age and sex were tested statistically for differences in terms of the level (mean value) and the pattern (amplitude and acrophase) of the curves using periodic analysis of covariance (PERCOVA). The periodic regression curve composed of 24- and 12-h periods was fitted satisfactorily to the measured BP values ($R^2=0.97$ for systolic BP and 0.98 for diastolic BP). The level of the periodic regression curve increased significantly with increasing age, being significantly higher in males than in females. The pattern of BP curve did differ among some age groups but not significantly between the sexes. (*Hypertens Res* 1992; 15: 127-135)

Key Words: normal blood pressure, blood pressure by age and sex, circadian rhythm, Fourier transformation, periodic regression curve

The diagnosis and treatment of hypertension is based on the determination of blood pressure (BP) in the physician's office. However, it has been pointed out that such casual BP measurements may not be the best method of evaluation. As an alternative ambulatory BP monitoring offers the potential advantage of improving patient care (1,2). Portable and noninvasive ambulatory BP monitoring devices for clinical use have been much improved technically in recent years (3). While it would be important to obtain accurate information about the diurnal variation of BP in healthy individuals (1,4-8), such data have not been collected in a large group of Japanese subjects. The present study was therefore carried out to clarify the characteristic features of the diurnal variation and rhythm of BP in 540 normal healthy Japanese adults.

Subjects and Methods

Subjects

We evaluated 540 healthy Japanese adults, 304 men and 236 women, ranging in age from 20 to 79 years, (mean 40.9 ± 12.8 years old; Tables 1, 2). They

were employees of our affiliated hospitals or of local businesses in Nagoya. All were free of cardiovascular disease and had no abnormalities in routine electrocardiogram, chest x-ray, blood chemistry, or urinalysis. Shift workers were not included in this study. Their mean casual systolic/diastolic BP was < 140 mmHg/ < 90 mmHg, determined on more than three different occasions. Informed consent for participation was obtained from all of the subjects.

Methods

The 24-h ambulatory BP and pulse rate (PR) were measured automatically using the ABPM-630 (Nippon Colin Co., Komaki) (9,10) for 25 h in 395 subjects or 49 h in 145 subjects at 30-min intervals. Measurements were begun between 8:30 and 9:30 AM. Criteria for deleting or editing BP readings were as follows (11,12): If two successive pressure readings differed by more than 50% without a concomitant alteration in the heart rate, the second measurement was rejected. About 5% of the data were discarded according to this criteria.

Any individual who was unable to sleep soundly because of the discomfort caused by cuff pressure or for any other reason was excluded from study. In

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addition, any case with a data deficit of ≥ 2 h or who required removal of $\geq 10\%$ of the raw data, was excluded from evaluation.

The averages of the BP and PR readings obtained during a 24-h period, day (from 7: 00 to 22: 30) and night (from 23: 00 to 6: 30) were expressed as the mean $\pm$ SD (standard deviation).

Measurements were obtained on weekdays during normal activities. During the 24-h or 48-h period, the subjects were instructed to avoid bathing, napping, drinking alcohol, taking part in excessive physical activity and mental stress. Forty-nine-hour continuous recordings were obtained in 145 of the 540 subjects [73 men and 72 women, mean age, 30.6 ± 9.2 years (men) and 32.1 ± 9.0 years (women)] to assess the reproducibility of the measurements.

BP values obtained by the oscillometric method were used for analysis in this study because the deficit in measurements was less than 4%. To avoid artifacts we discarded the first two measurements

obtained in the first hour after the placement of the monitoring device.

Periodic regression analysis was performed to obtain the best fit regression curve to the BP and PR measured in a 24-h period. The periodic regression curves by sex, age and their combination were tested statistically for differences in terms of the level (mean value) and the pattern (amplitude and acrophase) using periodic analysis of covariance (PERCOVA), an analytical method derived by modifying ANOCOVA (See Appendix).

The degree of fit of the periodic regression curve to the measured data was assessed by the coefficient of determination (R^2). The difference in the level or pattern of the periodic regression curves was considered statistically significant if a p -value was less than 0.01.

Periodic Regression Analysis

Periodic regression analysis was performed on the values obtained by the 24-h and 48-h measurements

Fig.1. Measured blood pressure and periodic regression curve in normals. SBP, systolic blood pressure; DBP, diastolic blood pressure; MESOR, midline estimating statistics of rhythm-adjusted mean.

Table 1. Clinical Characteristics of Study Population

	Men	Women	Total
<i>n</i>	304	236	540
Mean age (yrs)	41.2 ± 11.6	40.5 ± 14.2	40.9 ± 12.8
Obesity index (Broca, %)	103.7 ± 11.2	104.0 ± 14.5	103.8 ± 12.7
Wake-up time (hr)	6:42 ± 1.00	6:36 ± 0:54	6:42 ± 1:00
Retirement time (hr)	23:36 ± 1:09	23:00 ± 1:18	23:18 ± 1:15

Table 2. Study Population by Sex and Age Group

Age Group (yrs)	Men	Women	Total
20's	49	65	114
30's	93	41	134
40's	84	62	146
50's	53	37	90
≥60's	25	31	56

through 12-harmonics (1,2,3.....10,11,12) for the former, and 24-harmonics (1,2,3,...22,23,24) for the latter. One-hour mean values were used for the periodic regression analysis. Fourier transformation (13) was performed and the R^2 for each periodic component from the 1st (*i.e.*, 24-h period for 24-h measurement or 48-h period for 48-h measurements) to the 12th or 24th (2-h period for either measurements) was calculated for the transformed data (14).

The periodic regression curves with best fit to the values of 24-h or 48-h measurements were obtained using the appropriate number of periodic components with high R^2 (15,16).

Periodic Analysis of Covariance (PERCOVA)

PERCOVA was used to examine differences among periodic regression curves with multiple periodic components by applying the principle of periodic regression analysis and of analysis of covariance (ANOCOVA). The differences among periodic regression curves were examined in terms of two components independently, *i.e.* the level and the pattern. The constant in ANOCOVA corresponds to the level in PERCOVA, and the gradient in ANOCOVA to the pattern in PERCOVA.

Results

Periodic Regression Curve in All Subjects

The one-hour mean values of systolic BP and diastolic BP for 540 subjects measured at 30-min intervals throughout a 24-h period are plotted in Fig. 1 (solid circles connected with heavy line). Periodic regression analysis was performed on these values through 12-harmonics and the R^2 for each periodic component was determined. For the systolic BP, R^2 for 24-h and 12-h periods was 0.81 and 0.16, respectively, with a total of 0.97. The R^2 for periods less than 8-h was 0.03. For the diastolic BP, the R^2 for 24-h and 12-h periods was 0.79 and 0.19 respectively and the R^2 for periods less than 8-h was 0.02. For

PR, the R^2 for 24-h and 12-h periods was 0.77 and 0.16 respectively and the R^2 for periods less than 8-h was 0.07.

The periodic regression curves to the measured one-hour mean values derived from the equations composed of only a 24-h period (1-harmonic Fourier transformation) are shown in Fig. 1 ($R^2 = 0.81$ for systolic BP, $R^2 = 0.79$ for diastolic BP and $R^2 = 0.77$ for PR. (Figure not shown for PR.) The periodic regression curves derived from the equations composed of 24-h and 12-h periods (2-harmonic Fourier transformation) are shown in the same figure ($R^2 = 0.97$ for systolic BP, $R^2 = 0.98$ for diastolic BP, $R^2 = 0.93$ for PR).

In the 145 persons in whom continuous measurements of BP and PR were done for more than 48 h, periodic regression analysis revealed the R^2 for the 48-h period to be less than 0.01 for either systolic or diastolic BP or PR. Therefore, the periodic regression curves for BP and PR were obtained by an equation composed of 24- and 12-h periods in this study. The periodic regression curves for the first and second days for the BP and PR showed almost the same level and pattern; therefore the reproducibility of systolic BP, diastolic BP and PR was quite high.

The level or MESOR (midline estimating statistic of rhythm-adjusted mean) is also indicated in Fig. 1. The periodic regression curve for BP and PR composed of 24-h and 12-h periods consisted of two peaks, one before noon (first peak) and the other in the evening (second peak). The BP reached the lowest level, the first nadir, at around 3:00 and then increased sharply in the early morning at around the time of awakening. There was a dip in BP in mid afternoon, *i.e.*, the second nadir. The BP decreased sharply in late evening followed by the first nadir.

Blood Pressure Variation

The 24-h variation (mean ± SD) in the systolic and diastolic BP is shown in Fig. 2. For the systolic BP, the upper limit was about 120 mmHg at night and about 140 mmHg during the day. The lower limit for the systolic BP was about 85 mmHg at night and about 105 mmHg during the day. For the diastolic BP, the upper limit was about 70 mmHg at night and about 85 mmHg during the day. The lower limit for the diastolic BP was 50 mmHg at night and about 60 mmHg during the day.

When rhythm analysis is performed by the cosinor method which has only a 24-h period, three parameters *i.e.*, MESOR, amplitude and acrophase,

Fig.2. Periodic regression curves (mean $\pm$ SD) for SBP and DBP. Black dots connected by a solid line indicate the mean values obtained in all subjects.

Fig.3. Parameters for periodic regression curve.

are used to define the characteristics of a periodic regression curve. The periodic regression curve in this study, however, was composed of periods of 24-h and 12-h, resulting in two peaks and two nadirs. Therefore, the parameters that defined the characteristics of the curve have been arbitrarily designated as shown in Fig. 3.

The parameters that represent the pattern of periodic regression curves for systolic BP, diastolic BP and PR are shown in Table 3. The first peak (Peak Time I) for the systolic BP, diastolic BP and PR occurred at around 11:00, and the second peak (Peak Time II) for the same variables occurred at around 18:30. The first nadir (Nadir Time I) occurred at around 3:00, and the second one ("afternoon dip") at around 15:00. The level (or MESOR) was 117 mmHg for systolic BP, 70 mmHg for diastolic BP and 74 bpm for PR.

Periodic Regression Curve by Age and Sex

The periodic regression curves of systolic BP for men classified by age revealed a significant difference in terms of the level except for those between their 20's and 30's (Figs. 4, 5, Table 4). The BP level of those in their 40's was significantly ($p < 0.01$) higher than that of those in their 50's. The systolic BP pattern revealed significant differences between those in their 20's and 40's, 20's and 50's, 20's and ≥ 60 's, 30's and ≥ 60 's, and 40's and ≥ 60 's (Fig. 5).

The diastolic BP level differed significantly among men in all age groups. The level of diastolic BP increased with age but that of men in their 40's was significantly ($p < 0.001$) higher than that of men in their 50's. The diastolic BP pattern revealed a significant difference between men in their 20's and 50's, 20's and ≥ 60 's, 30's and ≥ 60 's, and 40's and ≥ 60 's (Fig. 5).

Periodic regression curves of systolic and diastolic BPs for women by age (Fig. 6) revealed that the level increased significantly with increasing age, except for the diastolic BP level between women in their 30's and 40's (Figs. 6, 7). The pattern of systolic and diastolic BP in women did not differ significantly between age groups.

With increasing age, the level of systolic and diastolic BP increased at all time periods, e.g. during the day and night and throughout the 24-h period (Table 3).

Discussion

There is growing evidence that the ambulatory BP can predict target organ damage more effectively than the casual BP (17, 18). However, the normal variation of BP during daily activities has not been studied extensively in large populations. Thus, it becomes important to establish standards for interpreting such ambulatory BP data.

Rhythm Analysis

There are many reports on the rhythm analysis of BP using various methods and the circadian rhythm of BP, both in normal healthy subjects (6, 19-24) and in hypertensives (22-27).

In this study, periodic regression analysis was performed to obtain the curve which best fit the measured BP or PR values. The analysis of R^2 for each periodic component for the periodic regression curve revealed that the curve based on 2-harmonic (24-h and 12-h) Fourier transformations best fit the

Table 3. Parameters of Periodic Regression Curve for SBP, DBP and PR

	MESOR	Peak I	Peak II	Nadir I	Nadir II	Peak TI	Peak TII	Nadir TI	Nadir TII
SBP	117	124	125	104	123	11:00	18:25	2:40	14:30
DBP	70	75	75	59	73	10:40	18:30	2:35	14:25
PR	74	82	81	60	79	11:00	18:35	2:50	15:24

Fig.4. Periodic regression curves for SBP and DBP in normal men by age.

measured BP or PR values. Therefore, the curve had two peaks and two nadirs with differing amplitudes, two peak times, and two nadir times which defined its characteristics. This information had not been described in depth in previous reports. The two nadirs in the diurnal variation of BP and PR seem to be closely related to physical and mental rest. The midnight nadir, nadir I, is induced by sleep and the afternoon dip, nadir II, may be related to the lunch time and coffee break.

The periodic analysis of covariance (PERCOVA) was developed from the modified ANOCOVA to compare differences between periodic regression curves in terms of their level and pattern. When the BP variation was fitted to the periodic regression

curve, its pattern was represented by two components: the amplitude (the peak and the nadir in this study) and the acrophase (time of the peak and of the nadir in this study).

Accuracy and Reproducibility of BP Variation

The accuracy of measurements obtained by using the ABPM-630 has previously been described (9, 10). Because of body movement or other factors, up to 5% of the readings were judged unreliable according to the criteria (28) cited in the Methods section so that they were discarded from analysis.

Reproducibility of the ambulatory BP over periods of 48 h (29, 30) and other reported data have shown that the average BP as well as the pat-

Fig.5. Multiple comparison (Scheffe) of level and pattern differences for systolic and diastolic blood pressure in normal men by age.

Fig.7. Multiple comparison (Scheffe) of level and pattern differences for systolic and diastolic blood pressure in normal women by age.

Table 4. Mean Systolic and Diastolic Blood Pressures in 24-h, Daytime and Nighttime by Sex and Age

		20's	30's	40's	50's	60's ≤	Total
SBP	Total						
	24h	112±9	115±9	120±14	121±16	127±15	117±13
	Day	117±10	120±10	125±15	126±16	131±16	122±14
	Night	103±9	106±10	109±14	111±17	117±15	107±13
	Men						
	24h	118±8	118±9	124±13	121±13	130±16	121±11
	Day	124±8	124±10	130±13	126±14	135±17	126±12
	Night	108±8	108±9	112±14	109±13	120±15	110±12
	Women						
	24h	106±7	110±7	113±13	119±19	124±14	112±13
	Day	110±7	114±7	118±13	123±19	128±14	117±13
	Night	98±6	101±9	105±14	111±20	115±15	104±14
DBP	Total						
	24h	66±6	68±7	72±9	74±10	74±10	70±9
	Day	70±6	72±7	75±10	75±10	77±11	73±9
	Night	58±8	61±7	64±9	65±10	68±10	62±9
	Men						
	24h	68±6	69±6	75±9	73±8	77±11	72±8
	Day	72±6	73±7	79±9	77±9	81±12	76±9
	Night	60±6	61±7	67±10	66±8	70±10	64±8
	Women						
	24h	62±5	65±5	66±7	70±11	72±9	66±8
	Day	65±5	68±5	69±7	72±11	75±9	69±8
	Night	55±5	58±6	60±7	64±12	66±9	59±8

tern of variation are reasonably reproducible (8, 31), as we have shown.

Normal Features of Systolic and Diastolic BP

The BP curve showed two peaks during the day with an intervening "afternoon dip." The BP was the lowest during sleep at around 3:00. Our study

showed that the blood pressure variation followed a circadian rhythm as has been suggested previously (5, 6, 19-24, 27).

We found the circadian rhythm of BP to be composed not only of a 24-h period but also of a 12-h period. The level (24-h average) of the systolic BP was 117 ± 13 mmHg and that of the diastolic BP was

Fig.6. Periodic regression curves for SBP and DBP in normal women by age.

70 ± 9 mmHg. The normal range of the circadian curve of BP was represented by the mean $\pm$ 1SD in this study. The criteria for the upper normal level of casual BP as recommended by WHO (1987) is 140/90 mmHg, which is reasonable judging from the 24-h ambulatory data observed in the present study of healthy Japanese.

Periodic Components

The R^2 for the two periodic components, *i.e.* the 24-h and 12-h periods, was similar for the systolic BP, diastolic BP and PR, which may imply that the BP and PR are similarly regulated by extrinsic and intrinsic factors.

Sex and Age Differences

Analysis of the systolic BP level in men by age group revealed significant differences between all groups except between those men in their 20's and 30's, indicating their similar activities and life styles.

A significant difference in the systolic and diastol-

ic BP patterns was more frequently seen between those men in their 20's, 60's and other age groups than among other age groups. This may be related to the difference in life style: a late nadir time I and peak time II in subjects in their 20's and an early nadir time I and peak time I in those over age 60.

These findings may be attributed to differences in awakening time and retirement time between age groups. The average wake-up time was 6:42 and 6:54 in subjects in their 60's and 20's, respectively. The average retirement time was 22:12 and 23:42 in subjects in their 60's and 20's, respectively.

The periodic regression curve for systolic and diastolic BP in women by age group revealed a significant difference in the level between all age groups except for the diastolic BP between those in their 30's and 40's. A significant difference in the pattern was not observed between any age group. This may be explained by the small difference in the peak time and nadir time as well as the amplitude among age groups.

Study Limitations

The measurements were performed every 30 min which limits the precise analysis of rhythm especially within 8 h. Although the monitoring device is silent, the pressure of the cuff may have disturbed the sleep of some subjects producing some artifacts.

The criteria for normotension were based on the casual BP which was uniformly set at SBP < 140 mmHg and DBP < 90 mmHg, without taking the subject's age into account. This may have caused the BP level of the younger groups to be erroneously higher than the true normal.

Clinical Implications

The physician must consider the cost-benefit relationship when beginning long-term treatment for hypertension (32). Whether the normal range of blood pressure obtained in the Japanese adults tested in this study is appropriate requires additional prospective study based on the long-term evaluation of mortality and morbidity. Also additional research is required to standardize methods for the ambulatory monitoring of BP and to better define the normal range including variables based on racial differences.

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Appendix

Periodic Analysis of Covariance (PERCOVA)

When the measured P quantities in time series data y ($y_{i1}, \dots, y_{ij}, \dots, y_{ip}, \dots$) observed at t ($t_1, \dots, t_j, \dots, t_p$) are present in a number of groups ($A_1, \dots, A_i, \dots, A_a$), m -term Fourier series is fitted ($2m \leq p$, $m+1$ term or higher is considered an error ϵ)

$$y = \frac{a_0}{2} + \sum_{k=1}^m \{a_k \cdot \cos(\frac{2\pi kt}{T}) + b_k \cdot \sin(\frac{2\pi kt}{T})\} + \epsilon \dots \dots \dots (1)$$

$$= A_0 + \sum_{k=1}^m A_k \cdot \cos(\frac{2\pi kt}{T} - \theta_k) + \epsilon$$

we have used the least squares estimates employing the least square method with linearization about x from Eq. (1), if the following are set:

$$\beta_0 = \frac{a_0}{2}, \beta_{2k-1} = a_k, \beta_{2k} = b_k$$

$$x_{2k-1} = \cos(\frac{2\pi kt}{T}), x_{2k} = \sin(\frac{2\pi kt}{T})$$

The linearized equation is transformed to multiple regression form using matrix and vector as follows:

$$y = X\beta + \epsilon \quad \text{Least square estimator: } \beta = [X'X]^{-1}X'y$$

In analysis of covariance (ANOCOVA) the following two different regression equations, (2) and (3), are fitted to the data and difference between them are tested by analysis of variance (ANOVA).

Regression equation by group (A_i)

$$y_{ij} = A_{0i} + \sum_{k=1}^m A_{ki} \cdot \cos(\frac{2\pi kt_j}{T} - \theta_{ki}) + \epsilon_{ij} \dots \dots \dots (2)$$

where $i=i, j=1, \dots, p$

Total regression equation ($A_1, \dots, A_i, \dots, A_a$)

$$y_{ij} = A_{0T} + \sum_{k=1}^m A_{kT} \cdot \cos(\frac{2\pi kt_j}{T} - \theta_{kT}) + \epsilon_{ij} \dots \dots \dots (3)$$

where $i=1, \dots, a, j=1, \dots, p$

ANOCOVA is obtained by transforming regression equations (2) and (3) to the above multiple regression form or periodic regression equation.

The calculated results are summarized in the PERCOVA table:

Parameter	Sum of Square(SS)	Degree of Freedom(DF)	Mean Sum of Square (MS)	F-value
Total Period	$S_{\beta T}$	$\phi_{\beta T}$	$V_{\beta T} = \frac{S_{\beta T}}{\phi_{\beta T}}$	$F_{\beta T} = \frac{V_{\beta T}}{V_R}$
Group Difference	S_A	ϕ_A	$V_A = \frac{S_A}{\phi_A}$	$F_A = \frac{V_A}{V_R}$
Non-Parallelism	S_D	ϕ_D	$V_D = \frac{S_D}{\phi_D}$	$F_D = \frac{V_D}{V_R}$
Residual	S_R	ϕ_R	$V_R = \frac{S_R}{\phi_R}$	
Total	S_T	ϕ_T		

Three parameters were tested for the following reasons:

1) The total period was tested to evaluate whether the total periodic regression equation was significant.

When $F_{\beta T} \geq F(\phi_{\beta T}, \phi_R, \alpha)$, it is significant with the level of significance α .

2) The group difference (or the level) was tested to evaluate the mean value in each group when the periodic regression equation by group was non-parallel.

When $F_A \geq F(\phi_A, \phi_R, \alpha)$, it is significant with the level of significance α .

3) Non-parallelism (or the pattern) was tested to evaluate whether the periodic regression equation by group was parallel.

When $F_D \geq F(\phi_D, \phi_R, \alpha)$, it is significant with the level of significance α .

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