Circadian Variation of Hemodynamics and Baroreflex Functions in Patients with Essential Hypertension

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It is well known that cardiovascular accidents such as myocardial infarction frequently occur in the morning, but their triggering mechanisms are not clear. The present study investigated circadian variations of hemodynamics and baroreflex functions. Twenty-three patients with essential hypertension were studied. Direct blood pressure (BP) and ECG were recorded by telemetry over 24 h, and then computer-analyzed. The pulse-contour method was used to measure cardiac output (CO) and total peripheral vascular resistance (TPR). The ratio of low to high frequency components (LF/HF) of the RR-interval on ECG was calculated by power spectral analysis. The baroreflex sensitivity index (BRI) was measured on the basis of the ratio ΔRR/ΔPs (ΔPs = spontaneous decrease in systolic BP, ΔRR = change in RR). Furthermore, 24-h BP changes were transformed algebraically into positive load component (PC) and negative load component (NC) by using a Windkessel model. The circadian variation of hematocrit (Ht) was also measured. The least squares method was used to determine the time at which the maximum and minimum value of each measurement occurred. Whereas the maximum values for BP and CO occurred in the evening (18:30, 17:00), the maximum values for TPR and LF/HF occurred between 06:30 and 08:00, and the minimum value for BRI occurred at 08:00. PC significantly correlated with Ps, heart rate, and CO (r = 0.81, 0.92, 0.67), and NC significantly correlated with BRI and LF/HF (r = 0.71, 0.64). PC (related to cardiovascular function) reached a maximum and NC (related to baroreflex function) reached a minimum in the late morning (11:00). Ht was highest immediately after the subjects got out of bed. These hemodynamic imbalances may negatively influence coronary blood flow in the morning. (Hypertens Res 1997; 20: 157-166)

Key Words: baroreflex, intra-arterial pressure, cardiac output, circadian variation

The incidence of hypertensive cardiovascular accidents, such as myocardial infarction (1, 2), stroke (3, 4), myocardial ischemia (5-7), arrhythmia (8, 9), and sudden death (10-12), follows a circadian rhythm, reaching a maximum in the morning and decreasing to a minimum at night. A number of different factors influence the circadian variation of cardiovascular accidents (13). Heart rate (14, 15), arterial blood pressure (BP) (16, 17), and catecholamine levels (18) have been shown to peak in the morning, indicating that coronary vasoconstriction may increase in the morning as well (19). Platelet aggregation (20, 21) has been found to increase upon getting out of bed in the morning. A decrease in fibrinolytic factors (22, 23) has also been observed at this time. However, little research has been devoted to changes in hemodynamics in the morning. In a previous study we observed that peripheral vascular resistance was greater in the morning than in the evening in patients with essential hypertension (24). Although other researchers have also reported higher forearm vascular resistance (25) and increased coronary artery tone due to sympathetic nervous activity in the morning (19), none have analyzed hemodynamics continuously over a 24-h period in hypertensive patients.

Changes in hemodynamics are suspected to influence vascular accidents. Therefore, the present study considered both direct BP measurements and detailed circadian variations in several hemodynamic variables and baroreflex functions over a 24-h period.

Methods

Subjects
Twenty-three patients (14 men, 9 women, aged 25 to 70 yr) with mild or moderate essential hypertension (Table 1) who had not previously received anti-hypertensive medication or who had discontinued such medication at least 2 weeks before the study were enrolled. All patients were hospitalized and given a diet containing approximately 7 g of sodium chloride daily. The resting BP of each patient exceeded 160/90 mmHg (systolic BP over diastolic BP) on three different occasions when measured at
the outpatient clinic. Routine checks such as endocrinological and radiological examinations were performed to exclude subjects with secondary hypertension. In all subjects, the ocular fundus findings were Keith-Wagner class I or II, renal function was within normal limits, and no cerebrovascular or cardiovascular complications were clinically discernible.

Sixteen patients were considered to have left ventricular hypertrophy on electrocardiography (26) or echocardiography (Devereux criteria) (27). Following a thorough explanation of the study, all subjects gave their informed consent to participate. The study protocol was approved by the Ethical Committee of the Department of Internal Medicine, Yokohama City University.

**Direct BP and Cardiac Output Measurements**

Intra-arterial pressure was measured, and the electrocardiogram (ECG) was continuously monitored by telemetry for 25 h, from 11:00 a.m. until 12:00 p.m. the following day. Mealtimes, bedtime, and recreational time were standardized according to the hospital schedule. In accordance with previously reported methods (28, 29), a Teflon catheter was inserted into the left brachial artery under local anesthesia before 11:00. The stiff-walled catheter was connected to a strain-gauge transducer (Statham P50, Gould Statham Instruments Inc, Hato Rey, Puerto Rico) attached to the chest wall at the level of the heart. The average overall resonance frequency of the combined system was about 20 Hz. BP was calibrated at 0, 100, and 200 mmHg both before and after measurement using a sphygmomanometer. To prevent coagulation, the catheter was continuously flushed with heparinized saline solution (2 ml/h) using a portable microinfusion pump (NEC Sanei Instruments, Ltd., Tokyo, Japan).

V5 leads were used for taking ECGs, which were telemetrically transmitted together with BP waveforms by means of a portable transmitter (Model 1429, NEC Sanei Instruments, Ltd.). Both paper and tape recordings (CR-31 portable tape recorder, TEACH Co., Ltd., Japan) were collected.

Using a Windkessel model (30, 31), we employed a previously reported pulse contour method (24, 32) for continuous, 24-h measurement of cardiac output. Through an analogue-to-digital converter, tape-recorded BP and ECG waves were input into a computer at a 1-KHz sampling rate and subsequently computer-processed to determine the beat-to-beat stroke volume. Since this method provides only relative changes in cardiac output, cardiac output was measured using the dye-dilution method with a densitometer (EW-90, Erma Inc., Tokyo, Japan) at 11:30 and at 20:30, in order to convert these values into absolute values. According to the dye-dilution method (29), the coefficient of variation for cardiac output was calculated to be 2.9 ± 3.1 (SD)%.

**Power Spectral Analysis of RR Interval**

To evaluate the activity of the autonomic nervous system, we studied the power spectrum of the RR interval using the maximum-entropy method (33). According to previous studies (34, 35), the high frequency component (> 0.15 Hz) is considered to correlate with cardiac vagal activity, and the low frequency component (0.03-0.15 Hz) is reduced by parasympathetic or sympathetic pharmacological blockade (36, 37). It has also been suggested that the low frequency component is a marker of sympathetic modulation (38), although not necessarily a specific one (39). Therefore, we defined low frequency components as those occurring in the 0.01 to 0.15 Hz range and high frequency components as those occurring in the 0.15 to 0.40 Hz range. The ratio of low to high frequency for the time series was calculated as an index of sympatho-vagal balance over 24 h at intervals of 30 min.

**Measurement of Baroreflex-Sensitivity Index**

In accordance with the method of Bertinieri et al. (40-42), samples were taken at instances of spontaneous lowering of systolic BP (ΔPs), when the RR interval had decreased for at least four consecutive heart beats. The gradient of ΔRR to ΔPs (ΔRR/ΔPs) was calculated and taken as the baroreflex sensitivity index (BRI). Using only values for which the coefficient of correlation between systolic BP and RR changes was greater than 0.85, we obtained 4 to 30 BRI values at 30-min intervals from each subject. Previous studies have shown that baroreflex sensitivity values obtained by this method show good agreement with those obtained by the drug-induced method involving injection of phenylephrine and nitroprusside (43).

**Method of Calculating Positive Load and Negative Load Components**

Changes in heart rate (HR) and blood pressure over a 24-h period take place not in a disorderly fashion, but are influenced by several conditions (44-48). For example, during nocturnal sleep, HR and BP in normotensive and hypertensive subjects would be expected to decrease and increase, respectively. However, the magnitude of these changes would be influenced by factors such as stress, medication, and diet. Therefore, it is important to consider the load components that drive these changes in order to understand the underlying mechanisms.
drop until they reach specific fixed baseline limits (28, 45, 46). We previously studied the characteristics of these baseline limits, which we have called base BP and base HR (46). The correlation coefficient (r) between systolic BP (Ps) and diastolic BP (Pd) is high during all 24 h (47) (r > 0.8). A linear relationship can be observed: $Ps = n \times Pd + c$ (where n and c are constants). $Pso, Pdo$ and HRo represent the 0.5% lower probability integral of Ps, Pd, and HR frequency-distributions during nocturnal sleep (45, 46) (between the hours of 22:00 and 05:00). Heart rate was obtained from the electrocardiograph RR interval, and its base value (RR0), corresponding to HRo, was determined. In addition, a significant, high coefficient of correlation was observed between Pd and HR (48). Accepting these 24-h BP and HR characteristics, we assumed that all Pd values take Pdo as their starting base and that their exponents can be expressed as follows:

$$Pd = e^{-A(RR0-RR)} \times Pdo,$$

(A = logarithmic gradient of diastolic pressure decay, RR = pulse-to-pulse interval of pressure waveform during waking time, RR0 = RR of base BP during sleep, $\varepsilon$ = discrepancy between Pd and Pdo $e^{A(RR0-RR)}$, Pdo = diastolic base BP during sleep).

A theoretical formula for the function of $\phi$ was determined according to the Windkessel model. Since the blood pressure wave decreases exponentially after closure of the aortic valve (49, 50), arterial pressure should theoretically drop to $Pd \times e^{-A(RR0-RR)}$ when RR interval is extended to RR0 (A = logarithmic gradient of diastolic pressure decay, RR = pulse-to-pulse interval of pressure waveform during waking time, RR0 = RR of base BP during sleep). The function $\phi$ was calculated by determining $a$ and $b$ by multivariate analysis between actual Pd and Pdo $e^{-A(RR0-RR)}$. Then PdE was calculated using the equation $PdE = \phi \times Pdo$. The right panel indicates a high correlation coefficient (r=0.99) between these two values (each point is the average of 3-min values). A = logarithmic gradient of diastolic pressure decay, Pd = diastolic BP, Pdo = base BP, RR0 = base RR, E = elastic modulus, R = vascular resistance.

A scattergram of the 24-h values of Pd and RR showed that at each point Pd and RR arose from Pdo and RR0 and were distributed in the vicinities of the Pdo $e^{A(RR0-RR)}$ and Pdo $RR0/RR$ curves (Fig. 2). This scattergram demonstrates a proportional relationship between the exponential function and the hyperbolic exponent, expressed as $e^{A(RR0-RR)} = (1 + A \times RR0)/(1 + A \times RR)$. With the use of this equation, the following formulae were developed algebraically (52):

$$\phi \approx e^{A(RR0-RR)} + a \times Pd \times RR/(Pdo \times RR0) - 1 \times b \cdots (2)$$

$$\varepsilon \approx Pdo[a \times Pd \times RR/(Pdo \times RR0) - 1 \times b] \cdots (3)$$

Multivariate analyses (least squares linear regression analyses) were performed on actual values from each subject, and the values of a and b, as well as the correlation between PdE and actual Pd values, were determined (52). For each subject, the value of “a” ranged between 0.89 and 1.14 with a mean of 0.97 ± 0.11 (SD), and “b” ranged between 0.02 and 0.12 with a mean of 0.07 ± 0.03. For each subject, the coefficient of correlation (r) between the actual Pd value and the PdE value, determined using the function PdE = $\phi \times Pdo$, was high, with r = 0.91 ± 0.02 (SD) (range 0.98 to 0.87) (Fig. 2).

Thus, it is assumed that most circadian Pd values can be considered as Pdo, the exponential function $e^{A(RR0-RR)}$, and the residual component “a $Pd \times RR/(Pdo \times RR0) - 1 \times b$” (Fig. 3). In the exponential function $e^{A(RR0-RR)}$, the Windkessel model...
employs the expression $A = E/R$ (where $E =$ elastic modulus and $R =$ vascular resistance). The $e^{E/R(RR_o - RR)}$ increases as heart rate increases, arterial elasticity increases, and peripheral vascular resistance decreases (vascular flow increases), thereby expressing cardiovascular function, with a consistently positive load. This component was therefore designated as positive load component (PC).

$$PC = e^{A(RR_o - RR)}$$

Conversely, $Pd \times RR/(Pd_0 \times RR_0) - 1$, which represents a large part of the residual component ($\epsilon$), is thought to be a function related to negative feedback regulation. Since this function is hypothesized to assume a negative value when baroreflex regulation is incomplete (52), it is designated as negative load component (NC).

$$NC = Pd \times RR/(Pd_0 \times RR_0) - 1$$

Unlike mean $Pd \times RR$ values, which remain relatively constant during both waking and sleeping hours (53), if the baroreflex BP-control function is lowered when the subject is standing, heart rate increases (RR decreases), the Pd value remains small, and the value of $Pd \times RR/(Pd_0 \times RR_0)$ becomes less than 1.

**Hematocrit**

Blood samples for determination of hematocrit were taken with the subject lying down, 30 min after going to bed (at 21:00) and at 6:00, and at 6:30, after the subject had been standing for 30 min. Further samples were taken at 9:00, 12:00, 15:00, and 18:00 with the subject either standing or seated. Hematocrit was measured for all samples, using an automatic blood cell counting device.

**Statistical Analysis**

Data from 24-h measurements were averaged at 30-min intervals to obtain mean and standard error (SE) for each 30-min period for each subject. To calculate an approximate least squares (fitted) curve when two harmonics (cycles) were postulated and to determine the times of maximum and minimum values, the MemCalc program (33) for nonlinear least squares regression analysis (Mem Calc 200/1,000 program, GMS Co., Ltd., Tokyo, Japan) was used. To evaluate the compatibility of the fitted curve, differences between real and theoretical values were calculated and averaged for the 24-h period as "residuals." A program from the Social Survey Research Information Co., Ltd., (Tokyo, Japan) was used to perform least-squares linear-regression analysis, analysis of variance (ANOVA), and linear multiple regression analysis. Unless otherwise stated, values are expressed as mean ± SD. Values of $p < 0.05$ were considered to indicate statistical significance.
Results

Circadian Variation in Blood Pressure

Results from the curve plotted with the use of the nonlinear least squares method showed a residual (mean of differences between real and theoretical values) of 0.1 ± 1.9 mmHg, indicating a suitable fit. Minimum systolic BP values occurred at 02:30, and maximum values at 18:45. Minimum diastolic BP values occurred at 02:30 and maximum values at 18:20 (Fig. 4). In the hospital environment, maximum values were observed in the afternoon (Fig. 4).

Cardiac Output and Total Peripheral Vascular Resistance

Observations of cardiac output (CO) and total peripheral vascular resistance (TPR) showed minimum CO values at 01:00, and maximum values at 17:00. Minimum TPR values were observed at 15:00, and maximum values at 08:00 (Fig. 4). Whereas CO elevation was slight in the morning, TPR tended to rise and appeared to exercise a greater influence on the increase in BP in the early morning (Fig. 4).

Circadian Variations in Heart Rate and RR Power Spectrum

Minimum HR values were observed at 01:20, and maximum values at 12:00 (Fig. 4). Although the ratio of the low- to high-frequency components (LF/HF) did not show good agreement with the fitted curve, an examination of the overall trend showed that minimum values occurred at 21:30, and maximum values occurred at 06:30, at the time of getting out of bed in the morning (Fig. 4).

Circadian Variation in Baroreflex Sensitivity Index

The minimum baroreflex sensitivity index (ΔRR/ΔPs), calculated according to the method of Bertini et al., was observed at 08:00 in the morning, although the fitted curve was bi-modal (Fig. 5).

Circadian Variations in Components of Blood Pressure Changes

Analysis of circadian variation showed that PC \[e^{A(\Delta RR)}\] reached a maximum at 11:00, and that NC \[Pd X RR/(Pdo X RRo) - 1\] reached a minimum at approximately the same time (Fig. 5). The coefficient of correlation (r) between circadian NC and BRI change was 0.71 (p < 0.001) (Table 2). Negative NC values in the morning are thought to be caused by inappropriate circulatory regulation. PC showed a positive correlation with cardiovascular load (blood pressure, heart rate, and cardiac output, as shown in Table 2), and this factor was maximum in the morning.

These results indicate that the mechanisms by which blood pressure increases in the morning may differ from the mechanisms that operate at other times.

Circadian Variation in Hematocrit

Hematocrit values increased during sleeping hours, and reached a maximum when the subject remained...
in a standing position after getting out of bed in the morning (mean increase from the level at 21:00 was 3 ± 4%) (Fig. 6).

Discussion

The invasive nature of our method, which involved arterial puncture, limited the subjects to a small number of mild or moderately hypertensive patients. Since the subjects were hospitalized, they all went to bed, arose, and ate meals at similar times. This regimen enabled us to obtain uniform data. Although some reports (16, 17) have shown that BP is highest in the morning, our BP data did not consistently show peak values in the morning hours. This discrepancy may have arisen because our subjects were hospitalized. Nonetheless, both blood pressure and heart rate showed their greatest increase immediately after getting out of bed in the morning. Increased blood pressure and heart rate are thought to impose a load on the blood vessels, and might trigger the rupture of atherosclerotic plaques (54), thereby causing the acute development of a cardiovascular event. We also investigated stress imposed on blood vessels by hemodynamic factors other than blood pressure and heart rate.

Table 2. Correlation Coefficients between 24-h PC/NC and Other Variables

<table>
<thead>
<tr>
<th></th>
<th>PC</th>
<th>NC</th>
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<tbody>
<tr>
<td>Systolic BP</td>
<td>0.806***</td>
<td>-0.338</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>0.765***</td>
<td>-0.261</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0.921***</td>
<td>-0.693***</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>0.674**</td>
<td>-0.310</td>
</tr>
<tr>
<td>Total peripheral vascular resistance</td>
<td>-0.699*</td>
<td>0.533*</td>
</tr>
<tr>
<td>Baroreflex sensitivity index</td>
<td>-0.229</td>
<td>0.708**</td>
</tr>
<tr>
<td>LF/HF</td>
<td>-0.467*</td>
<td>0.642***</td>
</tr>
<tr>
<td>PC</td>
<td>1.000</td>
<td>-0.673**</td>
</tr>
<tr>
<td>NC</td>
<td>-0.673***</td>
<td>1.000</td>
</tr>
</tbody>
</table>

BP, blood pressure; LF/HF, Ratio of low to high frequency components by RR-power spectral analysis; PC, $c^A(RR_0−RR)$; NC, $Pd×RR/(Pd_0×RR_0)−1$; where Pd, diastolic BP; Pd$_0$, base Pd during sleep; RR, pulse interval; RR$_0$, base RR during sleep; A, logarithmic gradient of diastolic pressure decay; PC, positive load component; NC, negative load component. ***$p<0.001$, **$p<0.01$, *$p<0.05$.

Fig. 5. Trendgram of 24-h mean baroreflex sensitivity index (BRI), positive load component (PC), and negative load component (NC) for all patients.
Circadian Hemodynamics

We found low cardiac output and increased peripheral vascular resistance in the morning. Quyyumi et al. (19) have reported that the cardiac ischemia threshold value is lowest at 08:00. This finding suggests that, as with forearm vascular resistance values (25), general arterial resistance changes in the same direction as that of the coronary artery. Low cardiac output and high peripheral resistance create a condition that is detrimental to coronary vascular flow. Veerman et al. (55) recently described the circadian profile of systemic hemodynamics. They measured beat-to-beat stroke volume by the pulse contour method (calculated using the Wesseling algorithm (31)), and found a 22% increase in TPR during the night as compared with daytime average, as well as a decrease in TPR in the morning. These results differ from the findings of the present study, but the subjects in the study of Veerman et al. were young normotensive men aged 18 to 32 yr who exercised in the morning, whereas the subjects in the present study were middle-aged or elderly hypertensive patients who stood passively during the early morning and performed usual daily activities (sitting, standing, or walking) throughout the day. Several studies of humans have examined systemic hemodynamics at various times during the day, and the results of these studies are contradictory. Miller and Horvath (56) reported a lower CO during the hours of sleep than was observed in the present study. Khatri and Freis (57) reported that CO decreased and TPR increased during the night, although not significantly. The results from these studies contrast with those of Bristow et al. (58), who reported no change in CO, although BP and TPR decreased during the night. We previously reported (32) that TPR decreased significantly during sleep (slow-wave sleep) in older hypertensive patients, but not in younger patients. Physical activity causes marked increases in BP, heart rate, and CO, and a decrease in TPR (59). During passive standing, CO is lower and TPR higher than when the subject is in a supine position (60, 61). Thus, differences in the circadian variation of hemodynamics can be influenced at least in part by body position, physical activity, and differences between subjects.

Circadian Variations in LF/HF and Baroreflex

While LF/HF peaked in the morning (24), BRI, an index of baroreflex sensitivity (39-42), was minimum in the morning. Although HF is thought to be related to parasympathetic nerve activity (34, 35) and LF to some component of sympathetic nerve activity (38), these relationships are not always proportional (39). Nonetheless, LF/HF can be a useful index for evaluating parasympathetic-sympathetic balance. High BRI values are observed during the night, when the subject is lying down, and these values decrease when the subject gets out of bed. Reduced baroreflex sensitivity is considered a risk factor for myocardial infarction (62). Van de Borne et al. (63) reported that morning awakening induced a pronounced decrease in arterial baroreflex sensitivity and the high frequency component of interbeat interval recordings. Dysfunction of autonomic nerve regulation in the morning is thought to be one of the triggering mechanisms of myocardial ischemia.

Circadian Variations in PC and NC

Based on the concept that blood pressure increases from base blood pressure (Pd₀), the formula Pd = Pd₀ × [PC + aNC + b], where a and b are constants, was postulated. Changes in PC and NC showed that PC = e⁻ᵃ[R(R-R₀)⁻¹] peaked in the late morning, when NC = Pd × RR/(Pd₀ × RR₀) reached a minimum. Since PC increases as heart rate increases, elastic modulus (E) increases, and vascular resistance (R) decreases (vascular flow increase: TPR increased in the early morning, but decreased in the late morning in the present study), PC is considered to be a positive factor in cardiovascular response. Conversely, when Pd does not increase because of insufficient baroreflex function, despite actions such as standing that activate the baroreflex and increase heart rate, NC values become negative (Fig. 7), although the time phases of BRI response and NC response are different and NC response results from various factors such as changes in stroke volume and total vascular resistance (65).

Since coronary blood flow increases in the diastolic phase of the cardiac cycle, a longer RR interval provides a greater advantage. In addition, an extreme reduction in Pd × RR is thought to diminish coronary blood flow (64). NC values, which correlate positively with BRI (Table 2), are thought to reflect baroreflex action in heart rate regulation, although the times of minimum values are different for NC and BRI.
Fig. 7. Relationship between baroreflex sensitivity index (BRI) and negative load component (NC). HR = heart rate, Ps = systolic blood pressure, Pd = diastolic blood pressure, \( \Delta RR = \) change of pulse interval, \( \Delta Ps = \) decrease in Ps, \( Pdo = \) base Pd (minimum Pd value during sleep). RRo = base RR (minimum pulse interval during sleep). A negative NC value results when the increase in heart rate and increase in Pd are insufficient, such as when the baroreflex control mechanism is incomplete on standing after several hours of lying (left panel).

Circadian Variations in Hematocrit and Hemodynamics

The nocturnal reduction in plasma volume and circulatory blood flow volume may be explained as follows. While lying in bed at night, the subject remains in repose and drinks no water for 8 to 10 h. Thus, an absolute reduction in plasma volume may occur during the night because water volume is lost in expired air, perspiration, and urine formation, causing a negative water balance in the early morning. This hypothesis is supported by the finding that central venous pressure declines (66) and hematocrit increases during the night (67, 68). Talan et al. (67) reported that cardiac output and total peripheral vascular resistance in monkeys reached their maximum early in the morning. The smaller plasma volume and, possibly, greater blood viscosity are speculated to contribute to the morning increase in the incidence of silent ischemia and catastrophic vascular events, such as sudden cardiac death, myocardial infarction, and stroke. Our data also suggest that in the presence of reduced plasma volume, hematocrit rises and viscosity may increase, reaching a maximum early in the morning. Moreover, hematocrit rises even higher as soon as the subject stands.

Rising and moving after several hours of lying in bed in association with reduced plasma volume blunts the rate of increase in cardiac output and the accompanying baroreflex-induced increase in BP, despite elevated sympathetic nervous activity and peripheral vascular resistance. This may contribute to Pd \( \times R_R \) becoming lower than sleep-time Pd \( \times R_R \). In addition, autonomic nervous activity may not respond fully in the morning, which is a transitional phase between an extended period of lying down (with increased parasympathetic nervous activity) and a period of action in an erect posture (with increased sympathetic nervous activity). Whatever the reason, an imbalance exists in autonomic nervous activity in the morning. Baroreflex regulation related to heart rate control is poor, and cardiac output fails to rise in proportion to the increase in peripheral vascular resistance. These factors, in addition to increased hematocrit (lower plasma volume), create a condition that negatively influences coronary blood flow more than at any other time. These hemodynamic characteristics may increase the risk of myocardial ischemia in patients with essential hypertension, left ventricular hypertrophy and atherosclerosis. Further clinical research is necessary to explore the effects of aging and of different pathological conditions on these findings.

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