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Circadian Variation in Baroreflex Sensitivity Evaluated by Beat-to-Beat Hemodynamic Change in Patients With Essential Hypertension

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Abstract

The mechanisms underlying the higher incidence of cardiovascular events in the morning were investigated by studying the circadian variation in hemodynamics and baroreflex sensitivity (BRS) in 20 untreated inpatients with essential hypertension. Direct blood pressure (BP) and heart rate (HR) were recorded using telemetry. Cardiac output (CO) was measured by the dye dilution method. Beat-to-beat stroke volume (SV) and total peripheral vascular resistance (TPR) were obtained using the pulse contour method. The coefficient of regression between HR and systolic BP (SBP) change (ΔHR/ΔSBP=Ahr) was calculated for in 5 consecutive heart beats during which BP decreased spontaneously and linearly ($r>0.9$). Similarly, the ΔSV/ΔSBP (=Asv) and ΔTPR/ΔSBP (=Atpr) were also measured, and the negative values of these coefficients (−Ahr, −Asv and −Atpr) were calculated. Comparisons between morning (6–11 *a.m.*) and evening (4–9 *p.m.*) values showed no significant difference in mean BP (122 vs 127 mmHg) and HR (72 vs 73 bpm). However, CO (3.7 vs 4.2 *l*/min), −Ahr (0.28 vs 0.43 bpm/mmHg) and −Asv (−1.5 vs 1.4 m*l*/mmHg) were lower in the morning than in the evening ($p<0.01$). In contrast, TPR (40 vs 34 mmHg/*l*/min) and −Atpr (1.2 vs −1.4 min/*l*) were higher in the morning than in the evening ($p<0.01$). These findings suggest that lower −Ahr and −Asv and higher TPR and −Atpr may cause stress to the cardiovascular system in the morning in patients with essential hypertension.

Key Words
circadian rhythm, baroreceptors, hemodynamics, hypertension, pulse contour method

INTRODUCTION

A prominent increase in the onset of cardiovascular events such as nonfatal acute myocardial infarction and sudden cardiac death in the morning has been reported[1–3]. The onset of acute myocardial infarction was most frequent between 6 *a.m.* and noon[4]. Although these reports did not consider whether the subjects were hypertensives or normotensives, previous studies such as the Framingham Study demonstrated that hypertension is an important risk factor for ischemic heart disease, heart failure, and stroke[5]. Many investigators who studied the mechanisms of cardiovascular events suggested that increased sympathetic activation[6], psychological stress[7], and plasma viscosity[8] were related to cardiovascular events. Circadian variation of platelet aggregability[9], plasma norepinephrine level[1], and plasminogen activator inhibition[10] was clearly demonstrated. Furthermore, baroreflex sensitivity is decreased in patients with acute myocardial infarction[11], and this is considered one of the important risk factors in the onset of cardiac events. However, the relationship between the circadian variation in

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baroreflex sensitivity and hemodynamics is not clear. We therefore studied the circadian variation in baroreflex sensitivity on the basis of the relationship between the changes in systolic blood pressure and three hemodynamic parameters; heart rate, stroke volume and total peripheral vascular resistance.

METHODS

Patients

This study included 20 untreated inpatients (13 men and 7 women) with essential hypertension aged 25–72 years [54.2±12.4<mean ±standard deviation (SD)>]. Blood pressure level was assessed by office blood pressure measurement, and patients with severe hypertension (diastolic blood pressure ≧115 mmHg) were excluded. Target organ damage was also assessed by electrocardiography, chest radiography, biochemical indices of renal function, and fundoscopic examination, and patients classified as WHO stage III were excluded. Three patients had mild renal dysfunction (serum creatinine =1.8–2.1 mg/dl) and two patients had cardiomegaly. Other patients showed no remarkable abnormalities in laboratory data. All patients had taken no antihypertensive medication for at least 2 weeks before the study. The patients' behavioral cycle in our hospital was standardized, by rising between 6 and 7 *a.m.*, not allowing the resting position during the day, and going to bed around 9 *p.m.* Routine diagnostic procedures were performed to exclude causes of secondary hypertension, and all patients were diagnosed as having essential hypertension. All patients gave informed consent to participation in the study.

Protocol

Telemetry method

To measure intra-arterial blood pressure, the brachial artery was punctured under local anesthesia and the catheter (radial artery catheterization set, 20G×4.45 cm : ARROW, U.S.A.) introduced and connected to a micro-infusion pump (NEC Sanei, Japan) supplying normal saline with heparin sodium (10 U/ml solution). Intra-arterial blood pressure measured by a pressure transducer (Statham P50 : GOULD, U.S.A.), electrocardiogram and electroencephalogram measurements were transmitted by wireless and recorded on magnetic tape (SR-31 Portable Data Recorder : TEAC, Japan) using the telemetry method[12] for 24 hours with the patients in an almost unrestricted condition. Calibrations of blood pressure were performed at 0, 100, and 200 mmHg using a sphygmomanometer, and blood pressure waves and electrocardiograms were recorded on magnetic tape.

Cardiac output measurement

Cardiac output was measured by two methods, the dye dilution method and pulse contour method based on the Windkessel model. In the dilution method (cuvette method using Dye Densitometer Model EW-90, Erma), the measurements were performed after patients had rested for at least 30 minutes in the supine position in the morning (6–11 *a.m.*) and evening (4–9 *p.m.*). One ml of dilution indicator (5 mg/ml indocyanine green solution; Daiichi Seiyaku) was rapidly injected followed by approximately 20 ml of normal saline solution through a catheter introduced into the cubital vein. Arterial blood was drawn using a pump at 0.6 ml/sec from the time just before the dye injection and continued for approximately 15 seconds. This measurement was performed at least twice with a 10-minute interval, and the values were averaged. Secondly, to supplement the sparse data obtained by the dye dilution method, stroke volume was calculated continuously for 24 hours using the pulse contour method which was based on the Windkessel model[13]. Digitized data (sampling rate=1 kHz) was used to calculate the integration of $P(t)-20$ during the cardiac cycle ($\int \{P(t)-20\}\, dt$), the slope of the logarithm of pressure versus time (A) and the vascular elasticity (E). To fix the E for each patient, the stroke volume measured by dye dilution method at the same time during the calibration was used. With these values, stroke volume was calculated by the following equation.

$$\text{stroke volume } (SV) = A/E \cdot \int \{P(t)-20\}\, dt$$

We previously studied the reliability of pulse contour method[14] as compared to dye dilution method and calculated cardiac output (CO) by pulse contour method, and found a good correlation between the two methods ($r=0.96$).

With the beat-to-beat change of stroke volume and mean blood pressure (MBP), the minute-to-minute change in total peripheral vascular resistance (TPR) was obtained using the following equation.

$$TPR = MBP / CO$$

Measurement of baroreflex sensitivity

In general, baroreflex sensitivity is calculated as the coefficient of regression between RR interval and systolic blood pressure[15]. Using a non-pharmacological method[16], the coefficient of regression between heart rate (HR) and systolic blood pressure (SBP) (ΔHR/ΔSBP=Ahr) was calculated when the latter was decreasing spontaneously for at least 5 consecutive heart beats. Similarly, the coefficients of regression between stroke volume and systolic blood pressure (ΔSV/ΔSBP=Asv) and between total peripheral vascular resistance and systolic blood pressure (ΔTPR/ΔSBP=Atpr) were calculated. The values were excluded from the later analysis if the correlation coefficient of the regression line was smaller than 0.9. Regarding the interpretation of these values, greater increase in heart rate, stroke volume, and total peripheral vascular resistance for a certain decrease in systolic blood pressure indicates greater sensitivity of the baroreflex. In other words, the smaller these coefficients are, the greater the baroreflex sensitivity is. Therefore, we used the negative values of these coefficients ($-$Ahr, $-$Asv and $-$Atpr) as indices of baroreflex sensitivity. Beat-to-beat changes in stroke volume and total peripheral vascular resistance were obtained by the pulse contour method described above. The number of baroreflex sensitivity values obtained every hour varied from patient to patient and from time to time. The mean number was 20±12 (mean±SD) per hour.

Statistical analysis

Comparison was made between morning (6–11 *a.m.*) and evening (4–9 *p.m.*) values using the paired *t*-test, and a value of $p<0.05$ was considered statistically significant. Data were expressed as mean±SD.

RESULTS

Circadian pattern of hemodynamics

Blood pressure and heart rate were increased during the daytime and showed no significant difference between morning and evening values (mean blood pressure 122±2.0 vs 127±2.2<mean±SD>mmHg, heart rate 72±1.2 vs 73±1.0 bpm) (**Table 1**). Cardiac output, however, was lower in the morning than in the evening (3.7±0.9 vs 4.1±0.8 *l*/min, $p<0.01$) and total peripheral vascular resistance was higher in the morning than in the evening (39.9±0.9 vs 34.2±0.4 mmHg/*l*/min, $p<0.01$) (**Table 1**).

Table 1 Comparison of hemodynamics between morning and evening

	Morning (6–11 *a.m.*)	Evening (4–9 *p.m.*)	*p* value
SBP (mmHg)	162±4.5	172±2.0	NS
DBP (mmHg)	101±2.1	104±2.0	NS
MBP (mmHg)	122±2.0	127±2.2	NS
HR (bpm)	72±1.2	73±1.0	NS
CO (*l*/min)	3.7±0.9	4.1±0.8	$p<0.01$
TPR (mmHg/*l*/min)	39.9±0.9	34.2±0.4	$p<0.01$

SBP=systolic blood pressure; DBP=diastolic blood pressure; MBP=mean blood pressure; HR=heart rate; CO=cardiac output; TPR=total peripheral vascular resistance.

Correlation between indices of baroreflex sensitvity

The values of 24-hour Ahr and 24-hour Asv showed a positive correlation ($r=0.53$, $p<0.01$). On the other hand, the values of 24-hour Ahr and 24-hour Atpr showed negative correlation ($r=-0.48$, $p<0.01$). These correlation coefficients were not great enough to confirm that Ahr or conventional baroreflex sensitivity are identical to Asv and Atpr.

Circadian pattern of the indices of baroreflex sensitivity

The negative values of the coefficients of the regression lines described above ($-$Ahr, $-$Asv and $-$Atpr) were shown to be indices of baroreflex sensitivity (**Fig. 1**). Comparison of these baroreflex sensitivity indices in the morning and evening showed that $-$Ahr and $-$Asv were smaller in the morning than in the evening ($-$Ahr 0.28±0.008 vs 0.43±0.012 bpm/mmHg, $-$Asv -1.5 ± 1.1 vs 1.4±1.4 ml/mmHg, $p<0.01$; **Fig. 2**). However, $-$Atpr was greater in the morning than in the evening (1.2±1.1 vs -1.4 ± 1.4 min/*l*; **Fig. 2**).

DISCUSSION

Many investigators have studied the relationship between acute cardiac events and autonomic nervous activities. The interactions between structural and functional abnormalities are considered to tend to develop fatal arrhythmias[17]. A decreased baroreflex sensitivity, as a functional modulation, may be important in the pathogenesis of sudden car-

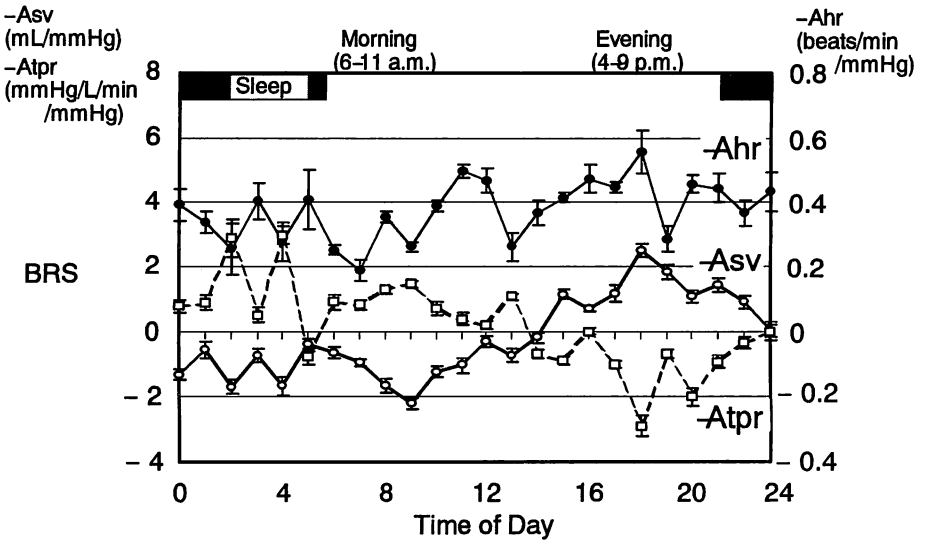

Fig. 1 Circadian pattern of baroreflex sensitivity (BRS) indices

The increases in HR, stroke volume (SV), and TPR during a decrease in SBP (ΔHR/ΔSBP=Ahr, ΔSV/ΔSBP=Asv, ΔTPR/ΔSBP=Atpr) are considered as indices of BRS. In other words, the smaller these coefficients are, the greater the sensitivity is. Therefore, negative values of these coefficients (−Ahr, −Asv, −Atpr) represent indices of BRS. Abbreviations as in Table 1.

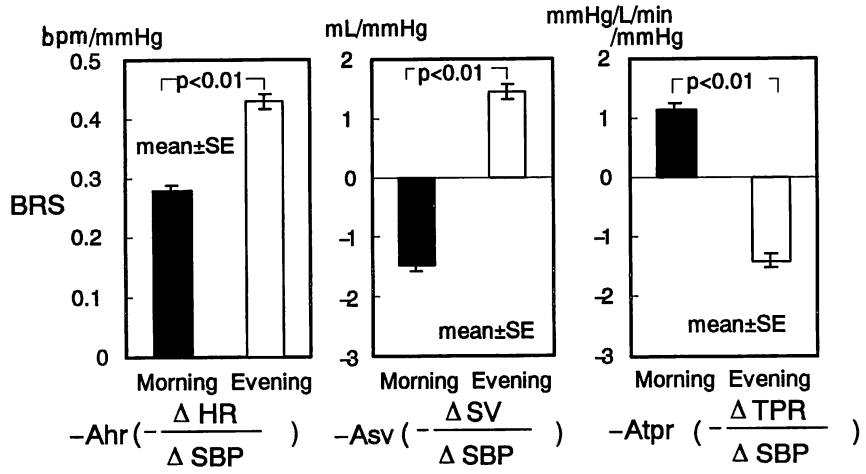

Fig. 2 Comparison of BRS indices between morning and evening

The indices of BRS (−Ahr, −Asv, −Atpr) in the morning showed lower sensitivity for −Ahr and −Asv and higher sensitivity for −Atpr than in the evening.
Abbreviations as in Table 1, Fig. 1.

diac death. In an experimental model[18], severe coronary vasoconstriction was observed within 2–3 minutes after elicitation of anger. Activation of the sympathetic nervous system was related to the vasoconstriction, which was prevented by stellectomy[19]. Baroreflex sensitivity is considered to be a marker of vagal reflexes[20]. Therefore, the low sensitivity represents high sympathetic nervous activity and increased coronary vasoconstriction, which is detrimental to the cardiovascular system. In a previous study[21], baroreflex sensitivity was compared before and 30 days after myocardial infarction in dogs, and these sensitivity values were reduced after infarction. The same study also demonstrated that post-infarct dogs with low sensitivity were more susceptible to sudden death than those with high sensitivity. Similar results were observed in humans[11,22]. Although ejection fraction is likely to be reduced in post-infarct patients, the attenuated baroreflex sensitivity was considered to be independent of the reduced ejection fraction because of the lack of correlation between these two variables[22]. In

our previous study[23], comparison of baroreflex sensitivity in the morning and evening demonstrated that the sensitivity was lower in the morning than in the evening.

In general, the coefficient of regression between systolic blood pressure and RR interval is used as the baroreflex sensitivity[15]. This conventional measurement of the sensitivity on the basis of the modulation of cardiac cycle may have a relationship to β-adrenergic and vagal activity, especially the cardiac vagal nervous system. However, we consider that the response of the autonomic nervous system to the change in systolic blood pressure may involve not only the β-adrenergic but also the α-adrenergic pathway. In our study, the index of baroreflex sensitivity determined from heart rate (−Ahr) is considered to be related to the conventional one determined from RR interval. Furthermore, we obtained the indices from measurements of stroke volume (−Asv) and total peripheral vascular resistance (−Atpr), independently. Regarding the interpretation of these indices, we consider that −Asv and −Atpr may be influenced by β- and α-adrenergic activity, respectively. Therefore, we could obtain more information on the response of the autonomic nervous system to the change of systolic blood pressure by these indices than by the conventional measurement of baroreflex sensitivity alone. Our results demonstrated that the values of −Ahr and −Asv were smaller in the morning than in the evening. On the other hand, the values of −Atpr were greater in the morning than in the evening. These data suggest that the β-adrenergic response to the change in blood pressure is attenuated and the α-adrenergic response is exaggerated in the morning. These changes in autonomic nervous system may be related to the reduction of peripheral and coronary blood flow accompanied by the increased vascular tonus.

Some previous studies reported that the increased α-adrenergic activity was related to coronary arterial spasm[24] and a fall of ischemic threshold[25]. A marked increase in catecholamine level was observed from 6 to 9 *a.m.* after awakening[9]. We also reported that serum norepinephrine was higher in the morning than in the evening[23]. Furthermore, some investigators suggested that the increased incidence of cardiovascular events in the morning may reflect a sudden rise of sympathetic activity and the reduction of vagal tone[26]. Similarly, our results are compatible with the previous reports which demonstrated an increased incidence of cardiac events in the morning.

CONCLUSIONS

1. We could obtain more information on the baroreflex response of the autonomic nervous system to the change of systolic blood pressure by measuring the changes in stroke volume and total peripheral vascular resistance, in addition to the changes in heart rate.
2. The influence of total peripheral vascular resistance on the baroreflex was considered to be greater in the morning. On the other hand, those of heart rate and stroke volume were considered to be lower in the morning.
3. These findings may be related to the higher incidence of cardiac events in the morning through exaggerated α-sympathetic nervous activity.

要　約

本態性高血圧症患者における循環動態からみた圧受容体感受性の日内変動

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急性心筋梗塞や心臓性突然死などの心臓血管発作は午前中に多く発症すると報告されている．その機序を解明するため，われわれは圧受容体感受性(BRS)と循環動態の日内変動を検討した．対象は未治療本態性高血圧症患者20例(男13例，女7例，平均年齢54±13歳)で，無拘束テレメーター法により，直接血圧，心拍数(HR)，脳波を記録し，色素希釈法により心拍出量を測定した．また，pulse contour法を用いて24時間の1回拍出量(SV)，全末梢血管抵抗(TPR)を1心拍ごとに求めた．さらに24時間の圧受容体感受性を求めるため，連続5心拍の自然降圧時における収縮期血圧(SBP)と心拍数，1回拍出量，全末梢血管抵抗の変化における回帰係数(ΔHR/ΔSBP＝Ahr, ΔSV/ΔSBP＝Asv, ΔTPR/ΔSBP＝Atpr)をそれぞれ求めた．この回帰直線は負の傾き

となるため，マイナスをつけて圧受容体感受性の指標とし（−Ahr，−Asv，−Atpr），午前（6–11 *a.m.*）と午後（4–9 *p.m.*）で比較した．

平均血圧（122 vs 127 mmHg），心拍数（72 vs 73 bpm）は午前と午後で有意差はなかったが，心拍出量（3.7 vs 4.2 *l*/min），−Ahr（0.28 vs 0.43 bpm/mmHg），−Asv（−1.5 vs 1.4 m*l*/mmHg）は午前のほうが午後より低く（$p<0.01$），全末梢血管抵抗（40 vs 34 mmHg/*l*/min）と−Atpr（1.2 vs −1.4 min/*l*）は午前のほうが午後より高かった（$p<0.01$）．圧受容体感受性の低下が心筋梗塞や突然死と関係するとの報告があるが，午前には−Ahrと−Asvが低く，−Atprと全末梢血管抵抗が高いことより，本態性高血圧症患者において，午前には血管抵抗の上昇に伴う相対的血流の低下と圧受容体を介する循環調節機能の低下がみられた．

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