Systemic Hemodynamics During Sleep in Young or Middle-aged and Elderly Patients With Essential Hypertension

Kohsuke Minamisawa, Osamu Tochikubo, Masao Ishii

Abstract Age-related changes in cardiovascular regulatory mechanisms may affect blood pressure homoeostasis during sleep and in the daytime. This study compared systemic hemodynamics during the daytime and sleep between 12 young or middle-aged patients (young, 42.1 ± 13.9 years old, mean ± SD, less than 56 years old) and 12 elderly patients with essential hypertension (old, 65.3 ± 2.6, 60 to 70 years old). They were all hospitalized and placed on a diet containing approximately 7 g sodium chloride per day. Intra-arterial blood pressure and electrocardiogram were recorded for 24 hours, and electroencephalogram and electrooculogram were recorded during the night with a telemetric method. Cardiac output was measured with patients in the supine position by the cuvette method during the daytime and stage 3 or 4 sleep at night. The averaged 24-hour blood pressure was similar in the two groups (140±2 [SEM]/85±3 mm Hg in the young group and 144±4/81±2 mm Hg in the old group). The reduction in mean blood pressure during sleep was also comparable in both groups (−18±2 in the young group and −20±2 mm Hg in the old group). Cardiac index was smaller in the old group than the young group during both the daytime and sleep (daytime, 2.3±0.1 versus 3.2±0.2 [L/min/m², P<.01; sleep, 2.1±0.1 versus 2.6±0.2 [L/min/m², P<.01]). The reduction in cardiac index during sleep was greater in the young than the old group (P<.05). Total peripheral vascular resistance index was elevated in the old group compared with the young group (daytime, 47.1±1.8 versus 36.2±2.6 mm Hg · min · m²/L, P<.01; sleep, 41.4±2.4 versus 36.1±2.1, mm Hg · min · m²/L, P<.05). Although the reduction in total peripheral vascular resistance index during sleep was not significant in the young group, it was pronounced in the old group, showing a significant group difference (P<.001). These findings indicate that different hemodynamic components are involved in the reduction of blood pressure during sleep in young and old hypertensive patients. (Hypertension. 1994;23:167-173.)

Key Words • hypertension, essential • blood pressure • sleep • hemodynamics • age factors

The recent development of portable devices for recording blood pressure has facilitated the monitoring of ambulatory blood pressure during a 24-hour period.1-5 It is clinically important to evaluate blood pressure at night, because some studies suggest that myocardial and cerebral infarctions occur not only in the daytime but also at night6-7; in other words, the occurrence of cerebral and cardiac events may be related to the circadian variation of blood pressure. Our previous study demonstrated that the hourly changes at night are still unclear. Some studies indicate that the nighttime blood pressure reduction is due to a decrease in total peripheral vascular resistance.1-5 whereas others suggest that it is caused by a decrease in total peripheral vascular resistance.1-5

To investigate the age-related changes in systemic hemodynamics, we recorded intra-arterial blood pressure for 24 hours and measured cardiac output during the daytime and nighttime in young or middle-aged and elderly patients with essential hypertension.

Methods

Subjects

The subjects consisted of 24 patients with mild to moderate essential hypertension, ranging in age from 16 to 70 years. They were all hospitalized and placed on a diet containing approximately 7 g sodium chloride per day. Their casual blood pressure at the outpatient clinic exceeded 160/90 mm Hg on three different occasions. Secondary hypertension and sleep apnea syndrome were excluded by careful history and thorough physical and laboratory examinations including radiological and endocrinologic studies. The subjects had hypertension of World Health Organization stage I or II and had not been treated or withdrawn from any antihypertensive agents for at...
least 2 weeks before the study. Informed consent was obtained from each patient before the study after the purpose and procedure of the study had been explained in detail. The protocol of the present study was approved by the Ethics Committee of the Second Department of Internal Medicine, Yokohama City University.

The subjects were divided into two groups by age: 12 young and middle-aged hypertensive patients who were less than 56 years old were categorized as the young group, and 12 hypertensive patients aged 60 years or older as the old group. The male-to-female ratio, body weight, height and surface area, and casual blood pressure in the outpatient clinic did not differ significantly between the two groups, but age did differ significantly (Table 1).

Methods

Intra-arterial blood pressure and electrocardiogram (ECG) were recorded continuously for 24 hours from 11 AM to noon the next day (the recording of the first hour was not used for analysis) with a telemetric method. According to the technique reported previously, a 20G PTFE catheter (4.5 cm long, Arrow) with a three-way connector was introduced percutaneously into the left brachial artery under local anesthesia before 11 AM. The catheter was connected to a pressure transducer (P10EZ, Gould Statham Instruments Inc, Hato Rey, Puerto Rico). Heparinized saline solution was continuously infused through the catheter at a rate of approximately 2 mL/h with a portable microinfusion pump (NEC-Sanei Instruments, Ltd, Tokyo, Japan) to prevent blood coagulation. Electrodes were attached to the left chest and sternum for recording of the ECG at V1. After having completed these procedures, we started recording intra-arterial blood pressure and ECG on open magnetic tape (SR31, TEAC Co Ltd, Japan) using a telemetry system (model 1429, NEC-Sanei) for 24 hours. Heart rate, which was calculated by measuring RR intervals, was also continuously recorded by the telemetric method. We asked patients to lie on a bed except while eating meals and going to the bathroom.

Electroencephalogram (EEG) and electrooculogram (EOG) were also recorded from before sleep (around 9 PM) to the next morning to identify sleep stages. Three electrodes were attached to the frontal and occipital regions and the ear to record EEG, and electrodes were also placed on both orbits to record EOG.

Cardiac output was measured with the cuvette method based on the dye dilution principle after patients had rested at least 30 minutes in the supine position, around 11:30 AM, and during sleep. For measurement of cardiac output, a cuvette was connected to the arterial catheter, 1 mL of indocyanine green solution (5 mg/mL; Daiichi Seiyaku, Ltd, Tokyo, Japan) was rapidly injected through a catheter introduced into the left cubital vein, and the dye solution was rapidly flushed with approximately 20 mL of saline solution. Arterial blood was drawn off using a pump at a rate of 0.3 mL/s from the time just before the dye injection and continued for approximately 15 seconds. The time course change of the dye concentration in the cuvette was monitored with a densitometer (EW-90, Erma Inc, Tokyo, Japan). Cardiac output was calculated according to the principle of Hamilton et al. with a computer. The measurement was performed twice with a 10-minute interval, and the two values were averaged. The coefficient of variation for the cardiac output measurement was 2.9±3.1% (SD). Cardiac index (CI) was obtained by dividing cardiac output by body surface area. Total peripheral vascular resistance index (TPRI) was calculated by dividing mean blood pressure (MBP) by CI. MBP was expressed as diastolic blood pressure plus one third of the pulse pressure.

The measurement of cardiac output during sleep was always performed after confirming that the patient was in stage 3 to 4 of sleep (moderate to deep sleep stages without eye movement) by checking the EEG and EOG. EEG was analyzed by a power spectrum analyzer (Power Spectral Analysis, Bennett Co, Tokyo, Japan) and a personal computer (NEC 9801, NEC-Sanei). In some patients who had sleep apnea, we did not measure cardiac output during the sleep apnea period.

An example is shown in Fig 1. Fig 2 shows heart rate, MBP, and an EEG analyzed by the power spectrum analyzer in a 46-year-old male patient.

Statistical Analysis

Measured variables are expressed as mean±SEM. Student's paired t test was used for intragroup comparisons of hemodynamic parameters between daytime and sleep, and Student's unpaired t test was used for comparisons between the young and old groups. Least-squares linear regression analysis was used to correlate two given parameters. Values of P<.05 were considered significant.

Results

Diurnal Changes in Blood Pressure

Intra-arterial blood pressure and heart rate were averaged every 30 minutes. Fig 3 represents the 24-hour intra-arterial blood pressure and heart rate profiles processed this way in the young and old groups. The 24-hour blood pressure and heart rate profiles were similar in the two groups. Table 2 summarizes the averaged intra-arterial blood pressure and heart rate values for the 24-hour period, daytime (6 AM to 9 PM)
and nighttime (9 PM to 6 AM). Although systolic blood pressure tended to be higher and diastolic blood pressure tended to be lower in the old group than in the young group at each period of the day, the differences were not significant. The degree of blood pressure reduction at night, i.e., the differences in systolic and diastolic blood pressures between daytime and nighttime, was similar in the two groups. Heart rate was not significantly different between the young and old groups in any period of the day. Heart rate decreased significantly during nighttime compared with daytime in the young and old groups (P < 0.01). Heart rate variability is shown in Table 3. There was no significant difference in 24-hour heart rate variability and its percent changes between the young and old groups, but the rate variability and its percent change in the young group during the daytime were greater than in the old group (P < 0.001).

Systemic Hemodynamics During the Awake State (Daytime) and Sleep

Table 4 summarizes the blood pressure, heart rate, and other hemodynamic parameters when cardiac output was measured with patients in an awake state (daytime, 11 AM to noon) and during sleep (around 1 AM). Systolic and diastolic blood pressures and heart rate during the daytime and sleep were not significantly different between the young and old groups. However, CI was significantly greater and TPRI was significantly smaller in the young group than the old group during both the daytime and sleep (Table 4). Systolic and diastolic blood pressures were definitely lower during sleep than during the daytime in both groups. The nocturnal reduction in heart rate was significant in the young group but not in the old group, in which it displayed only a tendency toward a reduction. As shown in Fig 4, the reduction in MBP (ΔMBP) during sleep was comparable in the two groups. However, the changes in CI (ΔCI) and TPRI (ΔTPRI) contrasted in the two groups. Although CI decreased significantly during sleep in both groups, its decrease was greater in the young than the old group (P < 0.05). On the other hand, TPRI decreased significantly in the old group but not in the young group, thus demonstrating a pronounced group difference (P < 0.001).

The percent changes in MBP during sleep (%ΔMBP) were related to the percent changes in CI (%ΔCI) and TPRI (%ΔTPRI). The correlation between the percent change in MBP and that in CI was significant in the young group but not the old group (P < 0.02), whereas the correlation between the percent change in MBP and

**Table 2. Averaged Intravascular Blood Pressures and Heart Rates for 24-Hour Period, Daytime, and Nighttime in Young and Old Groups**

<table>
<thead>
<tr>
<th></th>
<th>Young Group (n=12)</th>
<th>Old Group (n=12)</th>
<th>P (Group Difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>24-Hour</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>140±2</td>
<td>144±4</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>85±3</td>
<td>81±2</td>
<td>NS</td>
</tr>
<tr>
<td>Mean BP, mm Hg</td>
<td>105±2</td>
<td>102±3</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>77±3</td>
<td>79±2</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Daytime (6 AM to 9 PM)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>150±2</td>
<td>151±4</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>87±3</td>
<td>83±2</td>
<td>NS</td>
</tr>
<tr>
<td>Mean BP, mm Hg</td>
<td>108±2</td>
<td>106±2</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>79±2</td>
<td>82±2</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Nighttime (9 PM to 6 AM)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>135±3*</td>
<td>134±5*</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>82±2*</td>
<td>76±3*</td>
<td>NS</td>
</tr>
<tr>
<td>Mean BP, mm Hg</td>
<td>99±2*</td>
<td>95±3*</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>74±4*</td>
<td>75±3*</td>
<td>NS</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; bpm, beats per minute. Values are mean±SEM. 
1P < 0.05; 2P < 0.01 vs daytime.
that in TPRI was significant in the old group \( (P<.01) \) but not the young group (Fig 5).

**Discussion**

The purpose of the present study was to examine age-related hemodynamic changes, especially during sleep, in patients with essential hypertension. Some studies have shown that a J- or U-shaped relation exists between the occurrence of myocardial or cerebral infarction and blood pressure levels in elderly hypertensive patients, indicating the risk of an excessive fall in blood pressure. Indeed, we previously reported that the incidence of myocardial infarction in elderly hypertensive patients who had been administered antihypertensive agents was higher at night, especially between 1 AM and 3 AM, than during the daytime. Thus, it seems to be important to investigate the hemodynamic changes during sleep from a therapeutic point of view.

The present study was performed in patients with essential hypertension whose systolic blood pressure exceeded 160 mm Hg and diastolic blood pressure exceeded 90 mm Hg at the outpatient clinic before hospitalization. However, when the hemodynamic study was performed approximately 2 weeks after hospitalization, both systolic and diastolic blood pressures had decreased considerably in both the young and old groups. This may have been due to the effect of bed rest or salt restriction or both during hospitalization, as often experienced.

Many studies have been conducted to elucidate physiological changes during sleep such as the change in age-related hemodynamic changes, especially during sleep, in patients with essential hypertension. Some studies have shown that a J- or U-shaped relation exists between the occurrence of myocardial or cerebral infarction and blood pressure levels in elderly hypertensive patients, indicating the risk of an excessive fall in blood pressure. Indeed, we previously reported that the incidence of myocardial infarction in elderly hypertensive patients who had been administered antihypertensive agents was higher at night, especially between 1 AM and 3 AM, than during the daytime. Thus, it seems to be important to investigate the hemodynamic changes during sleep from a therapeutic point of view.

The present study was performed in patients with essential hypertension whose systolic blood pressure exceeded 160 mm Hg and diastolic blood pressure exceeded 90 mm Hg at the outpatient clinic before hospitalization. However, when the hemodynamic study was performed approximately 2 weeks after hospitalization, both systolic and diastolic blood pressures had decreased considerably in both the young and old groups. This may have been due to the effect of bed rest or salt restriction or both during hospitalization, as often experienced.

Table 3. Heart Rate Variability for 24-Hour Period, Daytime, and Nighttime in Young and Old Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Heart Rate Variability, bpm</th>
<th>Change of Heart Rate Variability, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime</td>
<td>14.9±0.2</td>
<td>9.5±0.4</td>
</tr>
<tr>
<td>Nighttime</td>
<td>8.3±0.2</td>
<td>9.5±0.4</td>
</tr>
</tbody>
</table>

Change of heart rate variability, %

<table>
<thead>
<tr>
<th>Group</th>
<th>Heart Rate Variability, bpm</th>
<th>Change of Heart Rate Variability, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime</td>
<td>14.4±0.7</td>
<td>13.6±0.7</td>
</tr>
<tr>
<td>Nighttime</td>
<td>20.3±0.2</td>
<td>16.5±0.7</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Heart rate variability means standard deviation of heart rate; percent change means standard deviation of heart rate divided by mean heart rate.
plasma norepinephrine concentration during non-REM sleep stages or changes in baroreceptor reflex sensitivity during sleep. However, only a few studies used suitable blood pressure monitoring methods during sleep. In the present study, the continuous intra-arterial blood pressure recording system we developed was applied to monitor the 24-hour blood pressure profile because this method does not disturb sleep, unlike noninvasive methods such as those involving inflation of an arm cuff. This procedure enabled the measurement of cardiac output using the cuvette method without discomfort to patients even during sleep. The measurement of cardiac output was performed after it was confirmed that the patient was in stage 3 or 4 sleep by checking EEG and EOG records.

The 24-hour profile of blood pressure was similar in the young or middle-aged hypertensive patients and the elderly hypertensive patients in the present study, with comparable blood pressure levels during a 24-hour period, daytime, and nighttime. The degree of blood pressure reduction during nighttime was also similar in the two groups. However, the nocturnal reduction in heart rate was significant in the young group and not in the old group, in which it displayed only a tendency toward a reduction. During the 24-hour period, heart rate variability was similar, but heart rate variabilities during daytime and nighttime were significantly different. Furthermore, two interesting differences in hemodynamic variables were also observed in the two groups. One was that CI was lower and TPRI was greater in the old group than the young group, both in an awake state and during sleep. The other was that the decrease in CI during sleep was significantly greater in the young group than the old group, whereas TPRI decreased considerably in the old group but not the young, thus demonstrating a definite difference in the change in TPRI between the two groups. It has been

### Table 4. Main Hemodynamic Parameters During Daytime and Sleep

<table>
<thead>
<tr>
<th>Young Group (n=12)</th>
<th>Old Group (n=12)</th>
<th>P (Group Difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daytime</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>153±4</td>
<td>157±7</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>88±3</td>
<td>81±3</td>
</tr>
<tr>
<td>Mean BP, mm Hg</td>
<td>109±3</td>
<td>106±3</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>62±1</td>
<td>62±3</td>
</tr>
<tr>
<td>Cardiac index, (L/min/m²)</td>
<td>3.2±0.2</td>
<td>2.3±0.1</td>
</tr>
<tr>
<td>TPRI, mm Hg · min · m²/L</td>
<td>36.2±2.6</td>
<td>47.1±1.8</td>
</tr>
<tr>
<td><strong>During sleep</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>124±3*</td>
<td>121±7*</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>73±2*</td>
<td>66±2*</td>
</tr>
<tr>
<td>Mean BP, mm Hg</td>
<td>91±2*</td>
<td>86±3*</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>56±3*</td>
<td>58±3</td>
</tr>
<tr>
<td>Cardiac index, (L/min/m²)</td>
<td>2.6±0.2*</td>
<td>2.1±0.1*</td>
</tr>
<tr>
<td>TPRI, mm Hg · min · m²/L</td>
<td>36.1±2.1</td>
<td>41.4±2.4*</td>
</tr>
</tbody>
</table>

Data are mean±SEM. BP indicates blood pressure; bpm, beats per minute; and TPRI, total peripheral vascular resistance index.

*P<.01 vs daytime.

Fig. 4. Bar graphs show changes in mean blood pressure (ΔMBP), cardiac index (ΔCI), and total peripheral vascular resistance index (ΔTPRI) in young and old groups. Changes in these variables were calculated on the basis of values obtained at the time of cardiac output measurement (Δ=value during sleep−value during awake state).

Fig. 5. Plots show percent changes (%=[value during sleep−value during awake state]/[value during sleep]) in mean blood pressure during sleep (%ΔMBP) correlated to percent changes in cardiac index (%ΔCI) and percent changes in total peripheral vascular resistance index (%ΔTPRI) in young and old groups.
The hemodynamic profiles observed in the present patients with essential hypertension with advancing age; been proposed for the nocturnal blood pressure reduc-

output. The mean age of their subjects was 48.5 years,

studies."

study seem to be consistent with the results of previous

middle-aged patients and decreased in elderly patients.

cardiac output is normal or increased in young or

explained by a decrease in sympathetic nerve activity. 23

During sleep was mainly due to a reduction in cardiac

output. The mean age of their subjects was 48.5 years,

similar to that of the young group in the present study.

On the other hand, Bristow et al15 suggested that the

blood pressure reduction during sleep was due to a

reduction in total peripheral resistance. The mean age of

their subjects was similar to that of the subjects in the

study of Khatari and Freis13 and the young patients in

the present study. Although the reason is not clear, the
difference in results between the study of Bristow et al15

and that of Khatari and Freis12,13 on ours seems to be due
to a difference in the clinical backgrounds of the subjects,
because the study of Bristow et al included severely

hypertensive patients with an average MBP exceeding

130 mm Hg and renal impairment.

It is assumed that diurnal variation of blood pressure

is mainly determined by sympathetic nerve activity;23,24; the

blood pressure reduction during sleep may be explained

by a decrease in sympathetic nerve activity. 23 Recent

studies that examined the age-related change in

sympathetic nerve activity by measuring plasma cate-

cholamine levels25 and muscle sympathetic nerve activ-

ity26 showed that sympathetic nerve activity is increased

in patients with essential hypertension compared with

normotensive subjects and that the activity is enhanced

with age in both hypertensive and normotensive individ-

uals. It has been suggested that there is a striking and

selective age-associated decrease in cardiac response to

sympathetic stimulation in laboratory animals.27,28 In

our study there was a significant inverse correlation

between age and CI (r = —.44, P < .05; Fig 6), and there

tended to be a positive correlation between age and

TPRI (r = .36, P < .1; Fig 6). Previous clinical studies

have also demonstrated a linear decline in maximal

work capacity and maximal oxygen consumption with

aging29 and that a decreased cardiac response to sym-

pathetic stimulation may occur despite elevated circu-

lating catecholamines in the aged.30 Thus, the differ-

ences in systemic hemodynamic changes during sleep

seen in the young and old groups in the present study

may be explained in part by the age-related alteration in

cardiac response to sympathetic nerve activity.

Other factors may be involved in the different homo-
dynamic changes during sleep in young or middle-aged

patients and elderly patients. For example, although

plasma renin activity was not measured in the present

study, the putative lowered circulating angiotensin II

levels in the elderly hypertensive patients31,32 may have

facilitated vasodilation of the resistant vessels in accor-
dance with a decrease in sympathetic nerve activity
during sleep, because the renin-angiotensin system is

known to be closely linked with the sympathetic nervous

system and because angiotensin has been confirmed to

activate, centrally and peripherally, the sympathetic

nervous system.33,34 The age-related changes in these

various systems participating in cardiovascular homeo-
stasis may have been the reasons for the differences in

the hemodynamic changes during sleep between the

young and old groups.

In summary, the present study indicates that different

demodynamic components are involved in the blood

pressure reduction during sleep in young or middle-

aged hypertensive patients and elderly hypertensive

patients; a decrease in cardiac output mainly underlies

the blood pressure reduction during sleep in the former

and a decrease in total peripheral vascular resistance in

the latter. The more pronounced reduction in total

peripheral vascular resistance during sleep in the el-

derly hypertensive patients may contribute to preserv-

ing the blood flow to vital organs. These findings should

take into account when drug treatment is started in

elderly hypertensive patients, and it may be desirable to

avoid antihypertensive agents that decrease cardiac

output in this group of patients.

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Hypertension. 1994;23:167-173
doi: 10.1161/01.HYP.23.2.167

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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