Hemodynamic Changes During Sleep in Hypertensive Patients

By Ibrahim M. Khatri, M.B., B.S., and Edward D. Freis, M.D.

SUMMARY

Hemodynamic studies were carried out during non-sedated all-night sleep on 14 patients with established hypertension. The significant changes from awake control values were as follows: mean arterial pressure fell 7.3% in stages I and II sleep and 8.8% in deep (stages III and IV) sleep; cardiac output decreased 10.3, 9.8, and 8.8% in stages I, II, and III and IV sleep, respectively; heart rate fell 4% in stage II sleep. Total peripheral resistance was not significantly altered. These hemodynamic responses during sleep were similar both quantitatively and qualitatively to those previously found in normal subjects. A small difference, which was of questionable significance, was noted between the two groups of subjects with respect to rapid eye movement sleep. While these observations do not disprove a primary neurogenic component in hypertension, they do not support such an hypothesis.

Additional Indexing Words:
Digital plethysmogram Rapid eye movement during sleep Nervous system activity

A fall in blood pressure during sleep in normotensive and hypertensive subjects has been demonstrated by several investigators. Hemodynamic studies performed during sleep in normotensive healthy subjects revealed that the reduction in arterial pressure was accompanied by a significant fall in cardiac output rather than in total peripheral vascular resistance. In addition, a decrease in sympathetic nervous system activity during sleep was indicated by changes observed during constant monitoring of the digital plethysmogram.

In essential hypertension, with the possible exception of early labile hypertension, there is a predominant rise in peripheral vascular resistance while cardiac output remains essentially unchanged. Sleep represents a basal state associated with reduction in cerebral and vasomotor activity. It may thus provide an approach to the evaluation of the neurogenic component, if any, in essential hypertension. The present study, therefore, was designed to determine the hemodynamic changes associated with sleep in patients with essential hypertension and to compare them with those found previously in normal subjects.

Methods

Hemodynamic studies were performed on 14 untreated male patients with essential hypertension. Their average age was 48.5 years with a range of 33 to 69 years. All patients had had persistently elevated diastolic pressure above 95 mm Hg for more than 1 year. Ten of the 14 showed left ventricular hypertrophy by electrocardiogram or chest x-rays. Two patients had grade 3 retinopathy, while the rest had grade 1 or 2 fundal changes. None had congestive heart failure at the time of the study. No sedatives or hypnotics were given and no food was permitted after 4 p.m. The nature of the procedure was explained to every patient in detail.

Methods used for recording hemodynamic events during sleep were similar to those reported in a previous communication. The patient slept in a soundproof room, and all recording equipment was kept in the adjoining room to prevent its disturbing the patient. The intra-arterial pressure, venous pressure, digital plethysmogram, frontoparietal and parieto-occipital electroencephalogram (EEG), and eye movements were simultaneously recorded on an eight-channel Sanborn recorder. Cardiac output (CO) was determined intermittently throughout the night.
Hemodynamic Changes in Various Stages of Sleep

<table>
<thead>
<tr>
<th></th>
<th>Awake control</th>
<th>Stage I</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>Mean</td>
<td>sd</td>
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<tr>
<td>MAP (mm Hg)</td>
<td>14</td>
<td>123.4</td>
<td>11.1</td>
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<tr>
<td>CO (ml/min)</td>
<td>14</td>
<td>7710</td>
<td>2480</td>
</tr>
<tr>
<td>TPR (dynes-sec cm⁻⁵)</td>
<td>14</td>
<td>1425</td>
<td>564</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>14</td>
<td>72.5</td>
<td>9.4</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>14</td>
<td>102.7</td>
<td>23.9</td>
</tr>
</tbody>
</table>

using central injection of indocyanine green (Cardio-Green) and withdrawal of arterial blood through a cuvette densitometer. The various stages of sleep were classified according to the schema of Dement and Kleitman5 with the exception of stages III and IV, which were grouped together.

Results were analyzed by the method of paired differences, which compares the values obtained in each stage of sleep with the pre-sleep control. Student’s t-test was applied to these differences.

Results

Mean Arterial Pressure (MAP), Cardiac Output (CO), and Total Peripheral Resistance (TPR)

A significant fall in arterial pressure occurred during all stages of sleep. The decrease in MAP during stage I sleep was 7.3% and during stage II 7.3%; the largest fall in stages III and IV sleep was 8.8% of the pre-sleep awake state.

In all stages of sleep the decline in arterial pressure was associated with a significant fall in CO (table 1). The decrease in CO from the awake control averaged 10.3% in stage I, 9.8% in stage II, and 8.8% in stages III and IV sleep. CO during stage I fell in six of seven observations and in II of 14 observations during stage II sleep. During deep sleep (stages III and IV) only one patient showed a rise in CO compared with the pre-sleep awake state. Changes in TPR were variable and not significant (table 1).

Heart Rate (HR) and Stroke Volume (SV)

No significant changes in heart rate occurred in the first stage of sleep. Of seven observations two were unchanged, two showed a rise, and the rest a fall. During the second stage of sleep a significant fall in heart rate occurred that averaged 4%. In deep sleep, (stages III and IV) heart rate rose in two patients, remained unchanged in two, and fell in the remaining six. No significant change in stroke volume occurred during any of the stages of sleep.

Hemodynamic Changes During REM Sleep (Table 2)

Cardiac output was determined during pressor episodes of rapid eye movement (REM) during sleep. In 13 episodes of REM sleep observed, MAP rose an average of 13.3 mm Hg from 109 to 122 mm Hg. This increase was associated with a significant rise in TPR averaging 354 dynes-sec cm⁻⁵ (P < 0.01). An insignificant fall in CO occurred, averaging 237 ml/min during 13 REM episodes; six were accompanied by a rise, and the rest by a fall, in CO. No significant changes occurred in heart rate or stroke volume during REM sleep.

Digital Plethysmogram

Periodic fluctuations of lesser frequency than the respiratory cycle, the so-called alpha and beta waves of the digital plethysmogram, were recorded during the awake state and were indicative of active sympathetic vaso-
HEMODYNAMIC CHANGES DURING SLEEP

<table>
<thead>
<tr>
<th>Stage II</th>
<th>Stage III-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>No. of patients</td>
<td>12</td>
</tr>
<tr>
<td>No. of observations</td>
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<td>12</td>
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</tbody>
</table>

Table 2

Hemodynamic Changes from Pre-REM to REM Sleep

| Mean art pressure (mm Hg) | 11  | 13 | 108.8 | +13.0 | 11.0 |
| Cardiac output (ml/min)   | 11  | 13 | 5412  | -1.8  | 14.7 | NS |
| Total peripheral resistance (dynes-sec cm⁻²) | 11  | 13 | 1703  | +20.6 | 16.4 | <0.01 |
| Stroke volume (ml)        | 11  | 13 | 75.3  | -2.5  | 15.7 | NS |
| Heart rate (beats/min)    | 11  | 13 | 72.1  | +1.0  | 14.0 | NS |

motor tone (fig. 1, left hand column). With the onset of sleep, digital volume and pulse volume increased while the large, low-frequency fluctuations (alpha and beta waves) in the digital volume diminished in amplitude. The middle column of figure 1 illustrates this change during stage III to IV sleep in one of the patients.

The onset of rapid eye movements usually, but not always, resulted in vasoconstriction and reduction in the volume of the digit, accompanied by an increase in the amplitude and frequency of alpha and beta waves and was indicative of increased sympathetic vasomotor activity. This change usually was associated with a rise in arterial pressure (fig. 1, last column).

Discussion

Whether the experimental procedure disturbed the patients sufficiently to prevent recording hemodynamic events that were truly representative of normal sleep is a pertinent consideration. With respect to this possibility, it should be noted that all of the recording equipment was in an adjacent room, and the patient was alone in a dark, soundproof room throughout the night, although he could communicate through an "intercom" if he so desired. The necessary leads and catheters also did not appear to disturb the patients unduly as indicated by the fact that the majority of them fell asleep within a short period. Indeed, it was difficult for some patients to remain awake long
enough to record the control determinations. The potentially most disturbing procedure was the CO determination since it involved sudden injection of dye and arterial sampling. However, when the venous catheter was placed centrally, the dye injection was not sensed by the patient. With regard to the blood sampling procedure, all manipulations, including the withdrawal into the cuvette densitometer, were accomplished outside the soundproof room. Questioning the patients following the awake control CO determinations revealed that they were not aware that any special procedures had been carried out. During sleep the EEG, which was always recorded during the output procedure, did not reveal in any instance a change in the sleeping pattern indicative of an alteration in the level of sleep.

Less assurance can be given regarding the observed cyclical pattern of all-night sleep. It was apparent that the movements of the patients were limited even during sleep, suggesting there was a subconscious awareness of the presence of the catheters. It should be emphasized, however, that the purpose of the present study was not to define the characteristic EEG pattern of sleep throughout the night in hypertensive patients, but rather to correlate hemodynamic changes with objectively documented levels of sleep. With respect to this objective the present experiments were successful in that hemodynamic measurements were obtained in all of the various stages of sleep and compared to the awake control. This information was then used as a basis for comparison with the hemodynamic changes previously observed in normal subjects during similar stages of sleep.1

The hemodynamic responses in sleep in the two groups, the normal subjects and hypertensive patients, were remarkably similar, differing only in minor details. Both groups showed

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**Figure 1**

Simultaneous recordings taken during wakefulness, deep sleep, and REM sleep from a 35-year-old man with essential hypertension. The digital plethysmogram shown above displays large amplitude fluctuations of digital volume in the awake state which are much diminished during deep sleep only to return with the onset of REM sleep. Pulse volume increases in deep sleep. See text for further details.
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an almost equal percentage of fall in blood pressure during the deeper stages of sleep. For example, the reduction of MAP during stages III and IV sleep averaged 8.5% in the normal subjects and 8.8% in the hypertensive patients. Although these changes seem to be of small magnitude, it should be noted that the awake control determinations were carried out with the patient alone, undisturbed, and resting quietly in the darkened, soundproof room. Thus, the intra-arterial pressures recorded during wakefulness probably approached the awake basal level.

Richardson and his associates observed during continuous 24-hour recordings of intra-arterial pressure that marked decrease of blood pressure occurred primarily between the highest daytime and lowest nighttime levels and that the difference between the lowest awake values and the sleeping levels was not large. They also did not find a significant difference between hypertensive and normal subjects with regard to the percentage of changes in blood pressure during sleep.

A minor difference between the two groups was observed in stage I sleep during which the fall of MAP reached statistical significance \( P < 0.001 \) in the hypertensive patients but did not do so in the normal subjects. This may reflect a somewhat greater responsiveness of the hypertensive's blood pressure to environmental influences.

Changes in CO also were similar in the normal subjects and hypertensive patients. Contrary to our initial impression, which had been based on a smaller series of observations, the fall in CO was significant in all stages of sleep in the hypertensive patients, whereas the reduction in TPR was not. This also had been the hemodynamic pattern observed in normal subjects. The magnitude of the changes in CO again was similar in the two groups. In stages III and IV sleep the fall in CO averaged 7.0% in the normotensive and 8.8% in the hypertensive patients.

Although TPR did not fall significantly, this does not imply that some vasodilatation failed to occur. If arteriolar caliber remained un-

changed in the presence of a reduced CO, then TPR would passively rise, and this did not occur. Also, a considerable degree of vasodilatation was observed in the digital circulation during sleep. The digital circulation, of course, may not be representative of changes occurring in the major vascular beds. Nevertheless, it is a sensitive index of sympathetic tone, and it indicated a depression of the latter during sleep. A reduced level of discharge from the vasomotor centers also was indicated by a decrease in the amplitude of the low-frequency alpha and beta waves of the digital plethysmogram during sleep as had been observed previously in normal subjects.

These observations indicate that in hypertensive patients, as in normal subjects, the onset of sleep is characterized by a reduced level of activity of the sympathetic nervous system. The latter, in turn, affects both the heart to reduce its rate and output and the microvasculature to produce moderate vasodilatation, the combined effects of which result in a reduction of blood pressure. The pattern appears to be the same in both hypertensive and normal subjects and also is of similar magnitude with regard to percentage changes.

Minor differences were present with respect to the REM sleep episodes associated with a rise of blood pressure. In the normal subjects the pressor episodes were accompanied by increases either in CO or TPR that were so variable that neither reached the level of significance. In the hypertensive patients there was a significant increase in TPR whereas CO exhibited variable changes, the average deviation being a slight but insignificant fall. However, it is not possible to consider these minor differences between the two groups as representing more than chance biologic variation.

The present results do not suggest that the hypertensive patient has any higher level of centrally induced vasomotor activity than the normal subject. If psychic influences were playing a major role in the maintenance of the hypertension, particularly in maintaining the
increased TPR, decline of the TPR during sleep might have been expected. Failure to observe such a change does not rule out a neurogenic component in the pathogenesis of hypertension, although it obviously does not support such an hypothesis. However, it is possible that different results might have been obtained if the subjects had been in the early, labile phase of hypertension rather than in the well-established phase of the disease.

References
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