

# Quantitative Analysis of the 24-Hour Blood Pressure and Heart Rate Patterns in Young Men

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To characterize the normal nycterohemeral blood pressure and heart rate profiles and to delineate the relative roles of sleep and circadian rhythmicity, we performed 24-hour ambulatory blood pressure monitoring with simultaneous polygraphic sleep recording in 31 healthy young men investigated in a standardized physical and social environment. Electroencephalographic sleep recordings were performed during 4 consecutive nights. Blood pressure and heart rate were measured every 10 minutes for 24 hours starting in the morning preceding the fourth night of recording. Sleep quality was not significantly altered by ambulatory blood pressure monitoring. A best-fit curve based on the periodogram method was used to quantify changes in blood pressure and heart rate over the 24-hour cycle. The typical blood pressure and heart rate patterns were bimodal with a morning acrophase (around 10:00 AM), a small afternoon nadir (around 3:00 PM), an evening acrophase (around 8:00 PM), and a profound nocturnal nadir (around 3:00 AM). The amplitude of the nycterohemeral variations was largest for heart rate, intermediate for diastolic blood pressure, and smallest for systolic blood pressure (respectively, 19.9%, 14.1%, and 10.9% of the 24-hour mean). Before awakening, a significant increase in blood pressure and heart rate was already present. Recumbency and sleep accounted for 65–75% of the nocturnal decline in blood pressure, but it explained only 50% of the nocturnal decline in heart rate. Thus, the combined effects of postural changes and the wake–sleep transition are the major factors responsible for the 24-hour rhythm in blood pressure. In contrast, the 24-hour rhythm of heart rate may reflect an endogenous circadian rhythm, amplified by the effect of sleep. We conclude that modulatory factors different from those controlling nycterohemeral changes in blood pressure influence the 24-hour variation in heart rate. (*Hypertension* 1991;18:199–210)

Recent progress in medical technology has seen the development of fully automatic portable noninvasive blood pressure recorders that reliably monitor blood pressure and heart rate over periods of 24 hours and longer. The use of ambulatory blood pressure monitoring has improved our understanding of the remarkably wide intraindividual and interindividual variability that characterizes blood pressure in humans.<sup>1,2</sup> It has

already been demonstrated that adverse effects of high blood pressure on the heart were better correlated with mean 24-hour blood pressure levels than with casual blood pressure readings.<sup>3,4</sup> It is also well established that, under normal conditions, blood pressure is higher during the daytime than during the nighttime.<sup>5,6</sup> Whether these day–night variations are entirely due to changes in activity or are partially related to an endogenous circadian rhythm that persists under constant conditions is still a matter of controversy. Although some studies indicated that the level of physical activity has a predominant role in the nycterohemeral blood pressure and heart rate variations,<sup>7,8</sup> others have given contradicting results.<sup>9,10</sup> It has been argued that the reproducibility of the overall 24-hour blood pressure pattern in the face of variable study conditions supports the concept of a truly circadian component.<sup>11</sup>

Although the blood pressure-lowering effect of sleep has been recognized for a long time,<sup>12–14</sup> studies relating the overall 24-hour variations in blood pres-

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sure and heart rate to polygraphically recorded sleep have, to our knowledge, not yet been performed. In the majority of recent studies, the daytime and nighttime periods have been either arbitrarily defined at fixed hours for all volunteers or obtained from diaries kept by the subjects.<sup>1,15-17</sup> Moreover, in most studies, no attempt was made to standardize the social and physical environment. On the day of ambulatory monitoring, subjects followed their usual daily routine, implying a wide variety of activity levels and social constraints. Thus, accurate estimations of the relative contributions of sleep and circadian rhythmicity to the 24-hour changes in blood pressure and heart rate in controlled standardized conditions are not yet available, even in normal subjects. The definition of the normal 24-hour patterns in standardized and easily reproducible recording conditions is, however, a major prerequisite to the delineation of abnormalities associated with various forms of hypertension and cardiovascular diseases. Finally, the objective identification of pathological patterns needs to be based on a detailed quantitative characterization of the normal 24-hour variation. However, the vast majority of descriptions of 24-hour profiles of blood pressure and heart rate have been qualitative or based on visual examination of hourly means. The few quantitative approaches that have been proposed have been either criticized for obvious inadequacies<sup>18,19</sup> or have involved nonparsimonious models including eight to 10 different parameters.<sup>9,19,20</sup>

To obtain a quantitative description of the normal 24-hour variations in blood pressure and heart rate in standardized conditions and delineate the relative roles of sleep and circadian rhythmicity, we performed 24-hour blood pressure and heart rate monitoring in 31 healthy male subjects, who were submitted to the same physical and social environment, with simultaneous polygraphically recorded sleep. A computerized method for characterization of 24-hour temporal variations,<sup>21</sup> originally developed for the analysis of hormonal rhythms, was used to describe the patterns of blood pressure and heart rate with a small number of quantitative parameters.

## Methods

### Subjects

Thirty-one white male volunteers (mean age,  $24 \pm 5$  years [SD]; range, 17–36 years) participated in the study. All subjects were of normal weight, and none had any physical illness. They had no personal or family history of hypertension or psychiatric illness. They did not take drugs for at least 1 year before the study. No transmeridian travel was allowed for 3 months before the study. None of the subjects were shift workers. They all had a regular sleep-wake schedule and were screened for absence of major sleep complaints. On admission, all subjects underwent a physical examination and routine laboratory

tests. They gave informed consent and were paid for their participation in the study.

### Experimental Protocol

The protocol was approved by the ethics committee of our institution. All participants were studied in the Sleep Laboratory of the Department of Psychiatry, Hopital Erasme, Universite Libre de Bruxelles, Belgium. After 1 night of habituation to the laboratory environment, polygraphic sleep recordings were performed during 4 consecutive nights. The electrodes were positioned between 9:00 and 11:00 PM. Subjects went to bed at their usual bedtime, but those who had not retired by midnight were asked to do so. They were allowed to awake spontaneously in the morning. The electroencephalogram, electromyogram, and electro-oculogram were recorded on a polygraph (Mingograph, Siemens, Erlangen, FRG) at the rate of 15 mm/sec. For the electroencephalogram, occipital, central, and frontal leads were used. Sleep analysis was made by an experienced rater following the criteria of Rechtschaffen and Kales.<sup>22</sup> During the day preceding the fourth night of recording, ambulatory blood pressure was monitored using a noninvasive device (Medilog, Oxford Medical Ltd, Abingdon, UK). The subjects were equipped with the device between 8:00 and 9:00 AM. Blood pressure and heart rate were measured automatically every 10 minutes during the 25-hour period. The arm cuff was positioned on the nondominant arm (i.e., left arm for right-handed subjects and right arm for left-handed subjects).

During the daytime, the subjects were free to ambulate inside the hospital, sit in an armchair, watch television, play boardgames, and engage in conversations with visitors and staff. Recumbency and naps were not allowed. The subjects were required to take two 1-hour walks, one in the morning (between 8:30 AM and noon) and one in the afternoon (between 1:30 and 6:00 PM), either inside the hospital or in the immediate surroundings, if weather permitted. They were instructed to walk at a moderate pace and to avoid inclines as well as staircases. The subjects were asked to refrain from movement and to keep their arm immobile during each cuff deflation. Standard mixed meals of identical composition were served at breakfast (8:00 AM), lunch (12:30 PM), and dinner (7:00 PM). One cup of coffee was allowed at breakfast. During the rest of the day, only water was permitted.

### Sleep Analysis

Time in bed was defined as the total time of electroencephalographic recording and coincided with the period of recumbency. Sleep onset and morning awakening were defined, respectively, as the times of the first and last 20-second intervals scored as I, II, III, IV, or rapid eye movement (REM) sleep stages. The sleep time period was defined as the time interval separating sleep onset from morning awakening. The total sleep time was defined as the

**TABLE 1. Sleep Electroencephalographic Measures (mean±SD) During 4 Consecutive Nights in 31 Healthy Young Men**

Sleep EEG measures	Night 1	Night 2	Night 3	Night 4 (ABPM)	ANOVA
Time in bed (min)	493±53	506±43	496±30	481±39	NS
Sleep period time (min)	475±51	484±42	474±34	456±57	NS
Total sleep time (min)	434±60	450±47	435±33	413±69	NS
Sleep efficiency (%)	88±5	89±5	88±5	86±11	NS

EEG, electroencephalogram; ABPM, ambulatory blood pressure monitoring; ANOVA, analysis of variance.

difference between the sleep time period and the total duration of all nocturnal awakenings. Sleep efficiency is the ratio between the total sleep time and the time in bed.

### Statistical Analysis

For all recordings, the first hour of measurement was not included in the statistical analysis to eliminate possible artifacts related to the beginning of the experiment. All measurements that corresponded to a pulse pressure below 15 mm Hg or represented an isolated increase by more than 50% over the previous measurement were considered to be technical artifacts and were deleted from the data set. For each subject, at least 80% of valid blood pressure and heart rate measurements had to be obtained for inclusion in the study. For all recordings, the percentage of invalid data (missing plus deleted data) averaged  $5.0\pm4.6\%$  (SD). Deleted data points were replaced by linear interpolation between the previous and following measurements.

For each profile of systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate, the 24-hour mean level was calculated as the mean of all measurements obtained during the 24-hour study period. The nighttime mean was defined as the mean of all measurements obtained after sleep onset and before morning awakening. The daytime mean was defined as the mean of all other measurements.

For each individual profile of SBP, DBP, and heart rate, the overall 24-hour variation was quantified by building a best-fit curve based on periodogram calculations, a statistical methodology extensively described elsewhere.<sup>21</sup> This procedure provides a quantitative description of the long-term trends of the profile, independently of sporadic short-term variations. Briefly, the periodogram method consists of fitting a sum of sinusoid functions on the series of data and of selecting those that contribute significantly to the observed variation. The components found significant with a minimum probability level of 95% are summed to build the best-fit curve. Because the method aims at describing the slow-varying properties of the profile, only significant components with periods longer than 6 hours were retained for inclusion in the best-fit curve. As a consequence, the model underlying the method has a maximum of seven independent parameters, and the best-fit pattern can be unimodal, bimodal, or trimodal. The acrophases and nadirs are, respectively, the times of

occurrence of maxima and minima in the best-fit curve. The amplitude of the best-fit curve is defined as 50% of the difference between its maximum and its minimum and may be expressed in absolute measurement units (i.e., mm Hg or beats/min; absolute amplitude) or as a percentage of the 24-hour mean level (relative amplitude). The level of an acrophase (nadir) is defined as the level of the best-fit curve at the time of occurrence of the acrophase (nadir).

### Statistical Tests

Differences between parameters characterizing SBP, DBP, and heart rate were evaluated by analysis of variance. The significance of pairwise contrasts was estimated using the Dunnett *t* test. The possible existence of declining or ascending trends before going to bed or before morning awakening was investigated by examining if the slope of a linear regression differed significantly from zero. Correlations were estimated using the Pearson coefficient. Unless otherwise indicated, all group results are expressed as mean±SD.

## Results

### Sleep

Table 1 gives the mean values for the time in bed, the sleep time period, the total sleep time, and the sleep efficiency obtained during the 4 consecutive nights after the night of habituation. Ambulatory blood pressure monitoring was performed during the fourth night. A comparison of the values obtained during the night of ambulatory blood pressure monitoring recording with the corresponding values obtained during the 3 preceding nights indicated that these parameters were not substantially affected by ambulatory blood pressure monitoring. The architecture of sleep during the 90-minute period preceding awakening was compared with that of a 90-minute period taken arbitrarily during midsleep. Before awakening, a significant increase in the duration of nocturnal awakenings (wake,  $p<0.05$ ) and a decrease in the duration of slow wave sleep (slow wave, stage III and IV,  $p<0.01$  for both) were observed. A trend to an increase in the REM period was also observed, but this increase did not reach significance ( $p=0.08$ ). Complete results of the sleep analysis will be reported elsewhere.

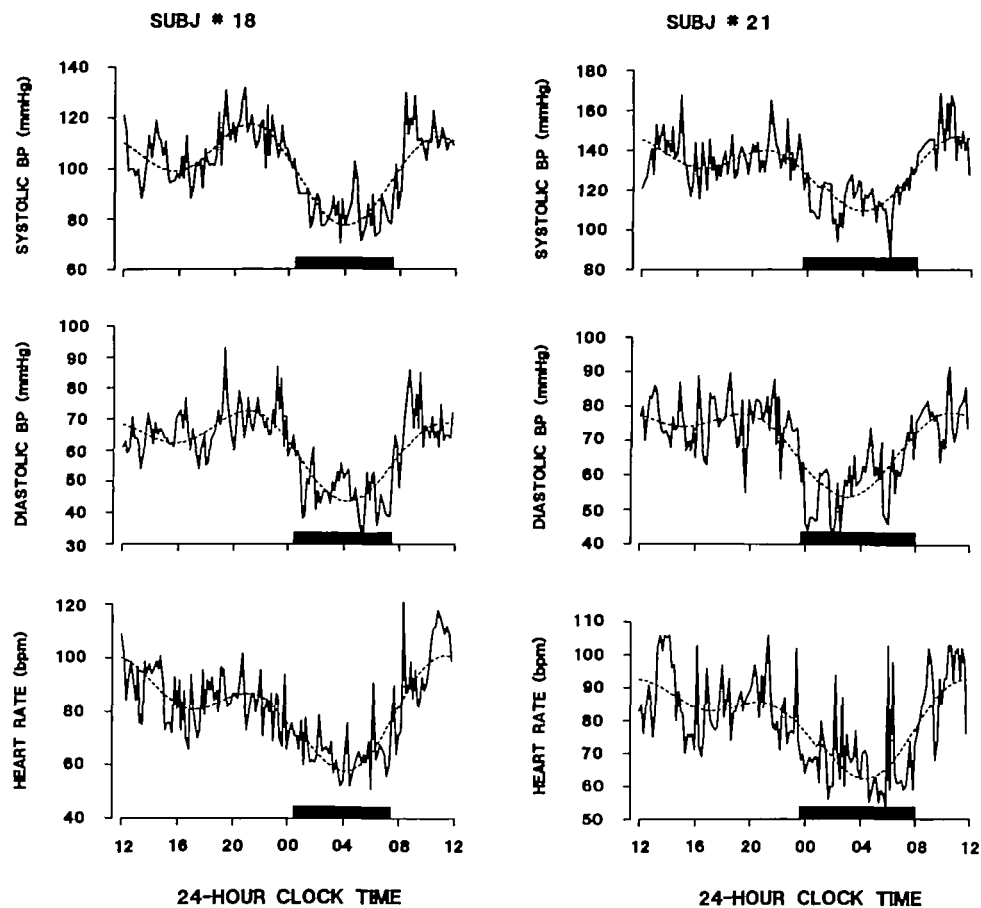


FIGURE 1. Representative recordings show 24-hour systolic (SBP) and diastolic (DBP) blood pressures and heart rate (HR) profiles in two subjects. Dotted lines represent best-fit curves. Black bars indicate sleep periods.

#### Quantitative Characteristics of the 24-Hour Profiles of Systolic and Diastolic Blood Pressures and Heart Rate

The 24-hour mean levels for SBP, DBP, and heart rate were  $106 \pm 9$  mm Hg,  $61 \pm 8$  mm Hg, and  $69 \pm 9$  beats/min, respectively. The daytime mean levels were  $111 \pm 10$  mm Hg for SBP,  $64 \pm 9$  mm Hg for DBP, and  $75 \pm 12$  beats/min for heart rate. During nighttime, a highly significant fall ( $p < 0.0001$ ) was observed for all three measures. Nighttime mean levels were  $96 \pm 8$  mm Hg for SBP,  $55 \pm 8$  mm Hg for DBP, and  $58 \pm 7$  beats/min for heart rate.

Based on the periodogram calculations, long-term trends were significant in 30 of 31 of the SBP profiles, in 30 of 31 of the DBP profiles, and in all heart rate profiles. A bimodal best-fit curve with a morning acrophase, a small afternoon nadir, an evening acrophase, and a profound nocturnal nadir was observed in the vast majority of profiles (i.e., 87% of all SBP, 81% of all DBP profiles, and 84% of all heart rate profiles). Figure 1 illustrates representative SBP, DBP, and heart rate profiles from two subjects. A few profiles were monomodal (three for SBP, four for DBP, and five for heart rate), with a single daytime acrophase located approximately midway between the morning and evening acrophases of bimodal patterns; a few were trimodal, with a small third

acrophase (two for SBP, five for DBP, and two for heart rate). The waveforms of the mean profiles of SBP, DBP, and heart rate, shown in the left panels of Figure 2, clearly reflect the bimodal nature of the great majority of the individual profiles.

Table 2 summarizes the quantitative characteristics of the 24-hour profiles of SBP, DBP, and heart rate derived from the periodogram analysis. On average, the overall amplitude of the 24-hour variation, when expressed as a percentage of the 24-hour mean, was smallest for SBP and largest for heart rate. The relative amplitude of the variation in heart rate was almost twice the amplitude of the variation in SBP. As shown in the right panels of Figure 2, these differences in relative amplitude of the 24-hour variation become clearly apparent when mean profiles are calculated after expressing each individual profile in percentage of the 24-hour mean. The timing of the morning acrophase varied between 10:00 and 11:00 AM, without significant differences between SBP, DBP, and heart rate. The relative value of the morning acrophase was highest for heart rate, intermediate for DBP, and lowest for SBP. The magnitude of the morning rise was characterized as the relative increase over the nocturnal nadir (i.e., calculated as the difference between the value of the

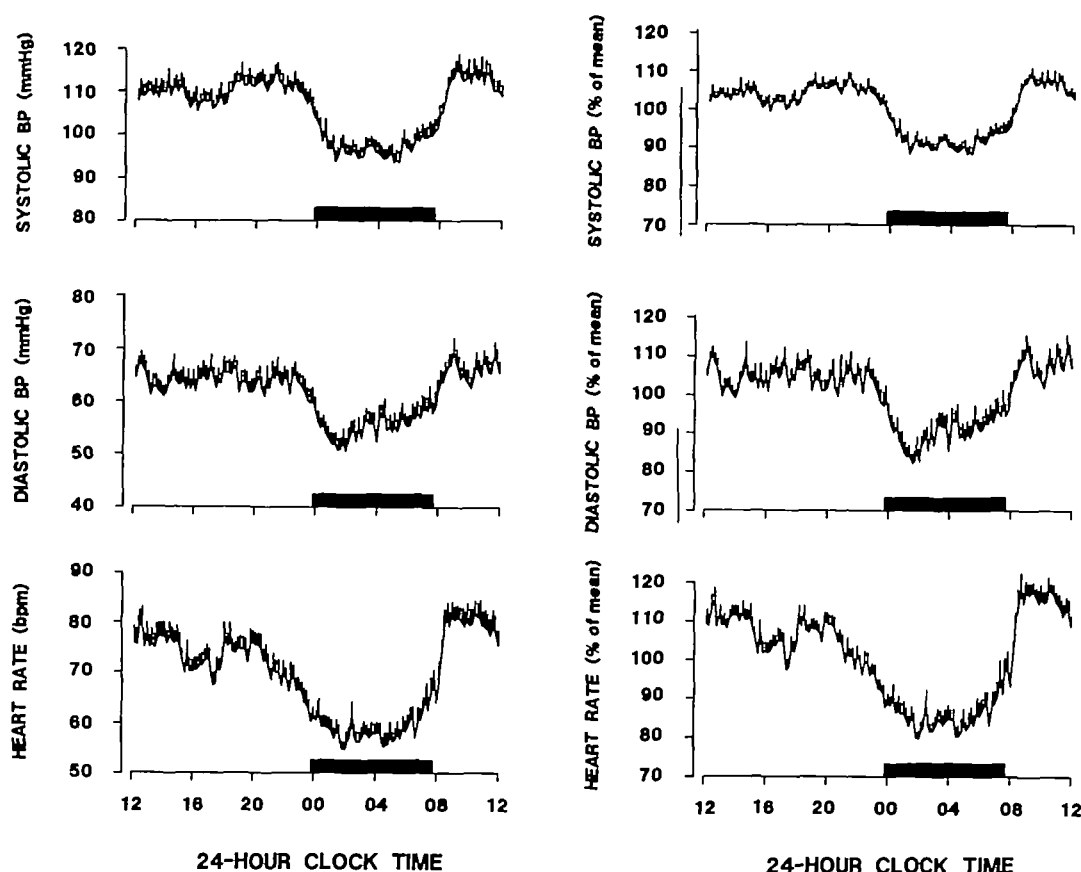


FIGURE 2. Representative recordings show transverse means, across individuals, of the 24-hour systolic and diastolic blood pressures (BP) and heart rate profiles expressed in absolute (left panels) or relative values (right panels). Black bars indicate sleep periods. Values reported are mean  $\pm$  SEM.

morning acrophase and the value of the nocturnal nadir, divided by the value of the nocturnal nadir). The magnitude of the morning rise was similar for SBP and DBP, averaging 20–30%, but was considerably greater for heart rate, averaging 51%. The midday nadirs occurred at similar times for SBP, DBP, and heart rate (around 3:00 PM) and were of similar value (approximately equal to the 24-hour mean level for all parameters). An evening acrophase was detected for all three variables around 8:00 PM but tended to occur approximately 30–50 minutes earlier for heart rate than for SBP and DBP. For heart rate, the evening acrophase was considerably lower than the morning acrophase ( $p < 0.0001$ ), indicating the existence of a declining trend during the daytime. In contrast, for SBP and DBP, morning and evening acrophases were of similar value. The magnitude of the nocturnal decline was expressed as percent decline from the evening acrophase (i.e., the difference between the value of the evening acrophase and the value of nocturnal nadir, divided by the value of the evening acrophase). The magnitude of the nocturnal decline was similar for SBP and DBP, averaging 19–23%, and was slightly more pronounced for heart rate, averaging almost 30%. A nocturnal nadir was reached around midsleep for

both blood pressures and heart rate but tended to occur 30 minutes earlier for DBP than for SBP and heart rate. The level of the nocturnal nadir was lower for heart rate than for SBP and DBP.

#### Effect of Bedtime and Sleep Onset

Mean bedtime and mean sleep onset occurred at 11:42 PM  $\pm$  34 minutes and 11:55 PM  $\pm$  32 minutes, respectively. Thus, on average, sleep latency was less than 15 minutes and, with a 10-minute sampling interval, effects of going to bed could not be differentiated from effects of falling asleep. In the left panels of Figure 3, the mean profiles of SBP, DBP, and heart rate were calculated using bedtime as a reference time point so that all values before bedtime were measured while the subject was still ambulatory. Immediately after bedtime, an abrupt fall in both SBP and DBP was observed (top left panels of Figure 3). A close-up on the period preceding and following bedtime is shown for SBP and DBP in the left panels of Figure 4.

Linear regression analysis indicated the absence of a significant declining trend (i.e., the slope of the regression line did not differ significantly from zero) in both SBP ( $p = 0.073$ ) and DBP ( $p = 0.31$ ) during the 90-minute period preceding bedtime. On aver-

TABLE 2. Quantitative Characteristics of the 24-Hour Variations in Blood Pressure and Heart Rate

Characteristics of BP and HR rhythms	SBP	DBP	HR	ANOVA	Pairwise contrasts		
					SBP-DBP	SBP-HR	DBP-HR
Amplitude (% of mean)	10.9±4.2	14.1±4.8	19.9±5.9	$p<0.0001$	$p<0.05$	$p<0.001$	$p<0.001$
Morning acrophase clock time	10:53 AM±01:22	10:02 AM±02:08	10:36 AM±00:55	NS	...	...	...
Value of morning acrophase							
Absolute	115±12 mm Hg	68±9 mm Hg	81±14 beats/min	...	...	...	...
% of mean	107.6±3.3	110.4±3.9	117.6±6.5	$p<0.0001$	$p<0.05$	$p<0.001$	$p<0.001$
Magnitude of morning rise (% increase over nocturnal nadir)	22.8±10.0	30.4±14.1	50.9±20.3	$p<0.001$	NS	$p<0.001$	$p<0.001$
Evening acrophase clock time	8:23 PM±1:06	8:00 PM±1:25	7:30 PM±1:11	$p<0.05$	NS	$p<0.02$	NS
Value of evening acrophase							
Absolute	116±10 mm Hg	66±7 mm Hg	75±11 beats/min	...	...	...	...
% of mean	108.4±3.6	110.3±6.1	108.9±6.2	NS	...	...	...
Magnitude of nocturnal decline (% decrease from evening acrophase)	18.8±7.0	22.5±9.3	28.6±8.9	$p<0.001$	NS	$p<0.001$	NS
Nocturnal nadir clock time	3:39 AM±1:14	2:54 AM±1:18	3:32 AM±1:17	$p<0.05$	$p<0.05$	NS	NS
Value of nocturnal nadir							
Absolute	93±9 mm Hg	52±9 mm Hg	54±7 beats/min	...	...	...	...
% of mean	87.3±4.9	84.3±6.2	78.4±6.7	$p<0.0001$	NS	$p<0.001$	$p<0.001$
Duration of nocturnal period (min)	447±68	407±114	460±69	$p=0.05$	NS	NS	$p<0.02$

BP, blood pressure; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; ANOVA, analysis of variance.

age, mean SBP levels during the 90-minute period after bedtime were  $11.9\pm7.2\%$  lower than during the 90-minute period before bedtime. The corresponding drop in DBP was of greater magnitude, averaging  $16.8\pm9.4\%$  ( $p<0.005$ ). When these figures are compared with the magnitude of the overall nocturnal decline, it appears that the effects of bedtime and sleep onset account for 65–75% of the total drop from evening acrophase to nocturnal nadir.

In contrast to blood pressure, the decline in heart rate appeared to start before bedtime, and a clear cut effect of bedtime or sleep onset was not readily apparent on visual examination (lower left panel of Figure 3). The top panel of Figure 5 shows a close-up on the period preceding and following bedtime for heart rate measurements. A decline in heart rate in the 4 hours preceding bedtime was found to be highly significant by linear regression analysis ( $p<0.0001$ ). From the slope of the regression line, the drop in heart rate during the 4 hours preceding bedtime averaged 13%. After bedtime, a further drop occurred. The mean heart rate level during the 90-minute period after bedtime was, on average,  $12.1\pm8.5\%$  lower than during the 90-minutes before bedtime. Thus, the approximately 28–30% overall nocturnal decline of heart rate (Table 2) corresponded to a 13–15% decrease while the subjects were awake during the evening followed by another 13–15% drop immediately after bedtime.

#### Effect of Morning Awakening and Getting Up

On average, the subjects woke up at 7:37 AM  $\pm 43$  minutes (end of polygraphically recorded sleep) and

got up at 7:40 AM  $\pm 43$  minutes. Thus, effects of end of sleep could not be differentiated from those of getting up. The right panels of Figure 3 depict the mean profiles of SBP, DBP, and heart rate calculated by using awakening time as a reference point. Awakening elicited clear rises in blood pressures and an acute increase in heart rate. A close-up on the 90-minute periods preceding and following awakening is shown for SBP and DBP on the right panels of Figure 4.

Linear regression analysis indicated that before the end of sleep, a progressive rise in both SBP ( $p<0.002$ ) and DBP ( $p<0.05$ ), averaging approximately 10 mm Hg for SBP and 5 mm Hg for DBP, was already present. After awakening, there was an additional significant rise of approximately 12 mm Hg for SBP and 7 mm Hg for DBP ( $p<0.001$ ). Thus, approximately 40% of the overall morning rise in SBP and DBP occurred during sleep, and the remaining 60% occurred after awakening. Heart rate also started rising before the end of sleep. The lower panel of Figure 5 shows a close-up on the period preceding and following awakening for heart rate measurements. Before the end of sleep, the slope of the regression line was significantly different from zero ( $p<0.01$ ). Awakening was associated with an abrupt and very large rise in heart rate that extended over approximately 30 minutes. After this rising phase of heart rate, the mean level during the next 3 hours represented an increase of  $29.5\pm18.2\%$  over the mean level during the 90-minute period preceding awakening. Thus, the approximate 50% morning rise in heart rate included a 30% increase related to awakening.

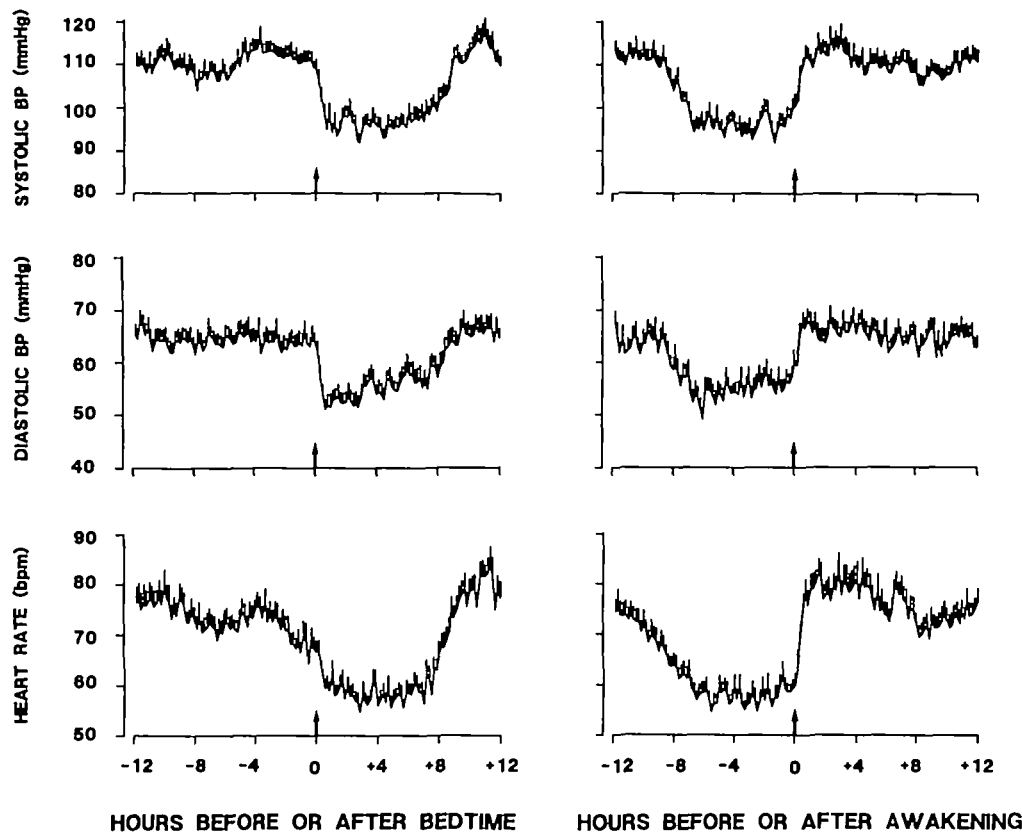


FIGURE 3. Representative recordings show transverse means, across individuals, of the 24-hour systolic and diastolic blood pressures (BP) and HR profiles. Data are referenced to time of sleep onset, shown by arrow (left panels) or time of morning awakening shown by arrow (right panels). Sleep onset and morning awakening are derived from the polygraphically recorded sleep. Values reported are mean  $\pm$  SEM.

#### Relation With the Sleep Parameters

To evaluate the duration of the period of low SBP, DBP, and heart rate, we defined the nocturnal period as starting at bedtime and ending when the best-fit curve reached 50% of the difference between the level at the nocturnal nadir and the level at the morning acrophase. For SBP and heart rate, the durations of the nocturnal periods were positively correlated with the time in bed (SBP,  $r=0.612$ ,  $p<0.001$ ; heart rate,  $r=0.701$ ,  $p<0.0001$ ), the sleep period (SBP,  $r=0.602$ ,  $p<0.001$ ; heart rate,  $r=0.620$ ,  $p<0.0001$ ), as well as the total sleep time (SBP,  $r=0.486$ ,  $p<0.01$ ; heart rate,  $r=0.604$ ,  $p<0.001$ ). The corresponding correlations for DBP were also positive but failed to reach significance. Sleep efficiency was not correlated with the nocturnal period of any of the three variables. The overall amplitude of the 24-hour variation in SBP, DBP, and heart rate was not correlated with any of the sleep parameters.

Figure 6 further illustrates the relations between sleep stages and variations in blood pressure and heart rate during sleep. The sleep period was divided into three equal parts, and the mean levels of heart rate and blood pressure during each third of the sleep period were calculated, together with the corresponding duration of wake, slow wave, and REM

stages of sleep. As the night progressed from sleep onset to morning awakening, there was a significant increase in amount of wake and REM, and a significant decline in amount of slow wave ( $p<0.001$  for all comparisons; right panels of Figure 6). Concomitantly, there was a significant increase in both SBP and DBP (third versus second third of sleep for SBP,  $p<0.05$ , and third versus first third of sleep for DBP,  $p<0.01$ ; left panels of Figure 6). Changes in heart rate tended to parallel the changes in blood pressure but failed to reach statistical significance.

#### Discussion

The rate of occurrence of a number of adverse cardiovascular events, such as myocardial infarction, sudden cardiac death, and stroke, exhibits a clear-cut increase in the early morning.<sup>23</sup> Among the possible causes for this temporal dependence, the concomitant rises in blood pressure and heart rate are often implicated.<sup>23</sup> Moreover, an inverse correlation between myocardial left ventricular mass index and percentage of nocturnal reduction of ambulatory blood pressure has been recently demonstrated.<sup>24</sup> Thus, there may be a relation between cardiovascular dysfunction and the pattern of changes in blood pressure and heart rate over the 24-hour cycle. To

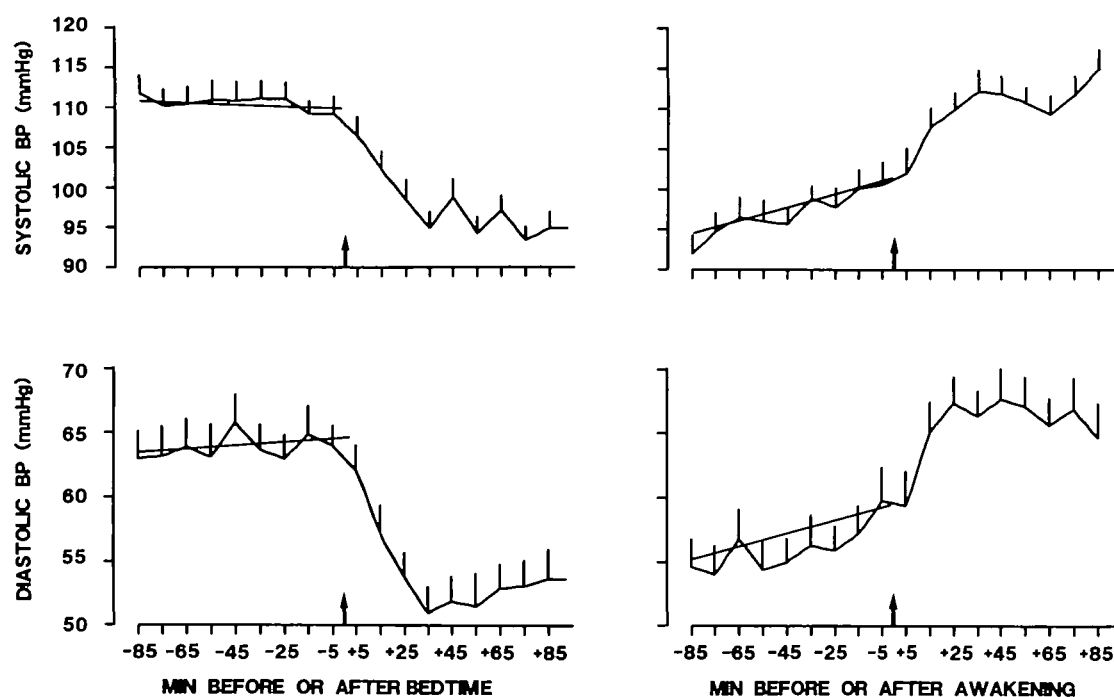


FIGURE 4. Close-up on the mean systolic and diastolic blood pressure (BP) values in the 90-minute period preceding and following bedtime, shown by arrow (left panels) or preceding and following awakening, shown by arrow (right panels). Straight lines across the mean systolic and diastolic BP values represent the regression lines. Values reported are mean  $\pm$  SEM.

further investigate this possibility, it is necessary to obtain a quantitative definition of normal nycterohemeral changes in controlled and easily reproducible conditions.

The major contribution of the present study is a detailed description of the 24-hour variations in SBP, DBP, and heart rate in a large group of healthy young men investigated in a standardized physical and social environment, with nighttime and daytime values identified based on polygraphic sleep recordings. The patterns of changes over the 24-hour period were quantified independently of the more rapid sporadic fluctuations that are known to affect blood pressure and heart rate, using a smooth best-fit curve that can be described with a limited number of parameters. This statistical procedure, which has been developed and extensively used in endocrinology, distinguishes significant rhythmic components from random fluctuations and is able to fully characterize nonsinusoidal profiles, such as those usually observed for blood pressure and heart rate. Thus, in the present study, the contribution of the sleep-wake/rest-activity cycle in causing the overall nycterohemeral variations in blood pressure and heart rate could be quantitatively defined instead of visually estimated. The results of this analysis provide an objective basis for the further delineation of the effects of sex, age, and pathological conditions.

The possible deleterious influence of noninvasive ambulatory blood pressure recording on sleep quality is regularly questioned.<sup>25</sup> Mancina et al<sup>26</sup> stressed that each device should be individually checked for their

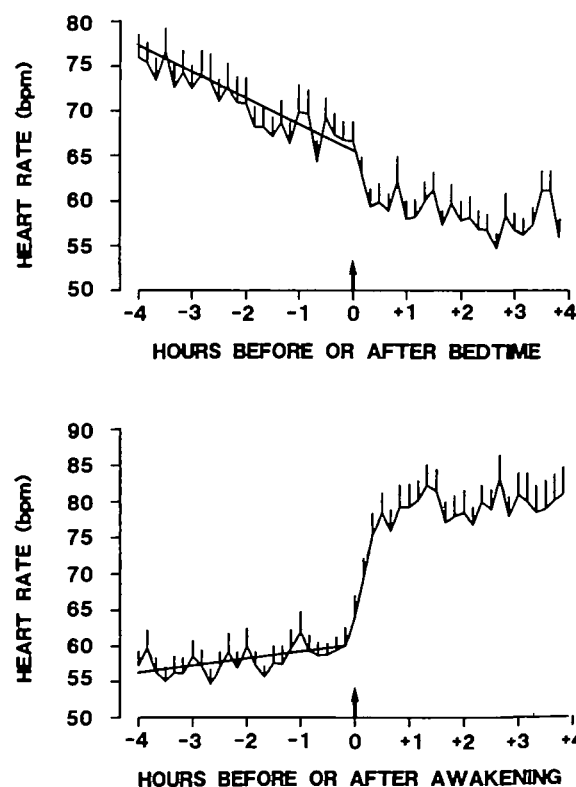


FIGURE 5. Close-up on the mean heart rate values in the 4 hours preceding and following bedtime, shown by arrow (upper panel) or preceding and following awakening, shown by arrow (lower panel). Values reported are the mean  $\pm$  SEM.



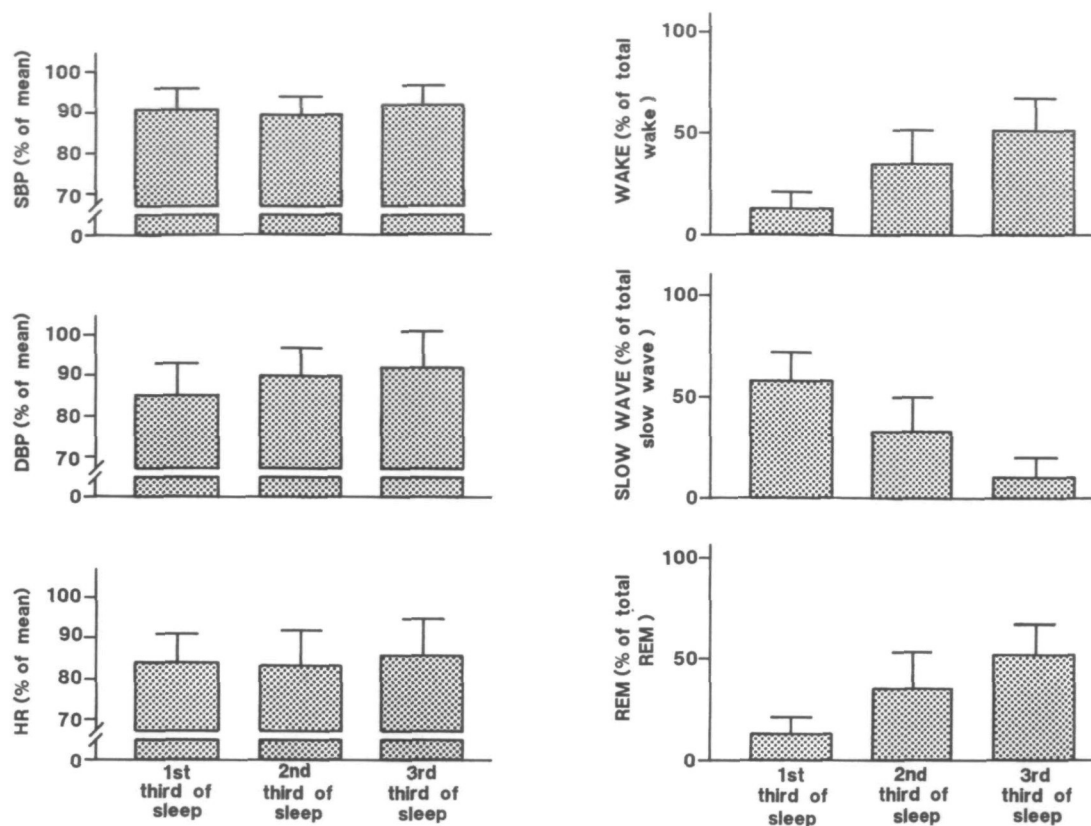


FIGURE 6. Bar graphs show evolution of the systolic (SBP) and diastolic (DBP) blood pressures and heart rate (HR) (left panels) and of the duration of nocturnal awakenings (Wake), slow wave sleep (SW), and rapid eye movement (REM) period (right panels) during the initial, middle, and last thirds of sleep. Blood pressure and HR were expressed in percentage of individual mean levels. Durations of Wake, SW, and REM were expressed as percentage of total duration of each of these stages. During last third of sleep, the increase in SBP was significant when compared with middle third ( $p < 0.05$ ) and the increase in DBP was significant when compared with initial third ( $p < 0.01$ ). No significant changes in HR were observed. For sleep measures, all comparisons between the three thirds of sleep were highly significant ( $p < 0.001$ ). Values reported are mean  $\pm$  SD.

possible disturbing effects on sleep quality. In the present study, sleep duration and efficiency were unaffected by blood pressure monitoring with the Medilog instrument. A preliminary analysis of the duration and distribution of sleep stages also indicates that the recordings did not significantly alter sleep architecture (J.P. Degaute et al, unpublished observations). Therefore, the characteristics of the 24-hour blood pressure and heart rate patterns reported here can be considered as representative of normal sleep-wake cycles.

Based on the periodogram calculations, a significant nycterohemeral variation was found in all but one case for SBP and DBP and in all cases for heart rate. When the 24-hour variation was not significant for SBP, the DBP and heart rate patterns of the same subject had significant long-term components. Similarly, when the 24-hour variation of DBP was not significant, the corresponding SBP and heart rate patterns had significant nycterohemeral variation. Thus, in this population of normal young men, the absence of 24-hour variation in either SBP or DBP seems to reflect technical problems or limitations in

the procedure for rhythm detection rather than a true pathology.

The normal pattern of 24-hour blood pressure and heart rate variations was found to be bimodal, with two daytime acrophases and a single nocturnal nadir. The mean quantitative characteristics of the nycterohemeral SBP, DBP, and heart rate variations are summarized in Figure 7. The bimodal nature of the patterns, which was objectively demonstrated in the present study by the best-fit curve, is also apparent on visual examination of previously published profiles.<sup>2,6,8,17</sup> Because these earlier studies involved different activity conditions, it appears unlikely that the bimodality of the blood pressure and heart rate nycterohemeral variation may reflect specific behavioral events. In particular, in the present study, the occurrence of the morning and evening acrophases was probably unrelated to the 1-hour walks taken by the subjects in the morning and in the afternoon. Indeed, the average timing of the second walk coincided with the afternoon nadir and the evening acrophase occurred much later, after the last meal. Although Mancina et al<sup>2</sup> have suggested that the afternoon nadir reflects the effects of sleep consistent

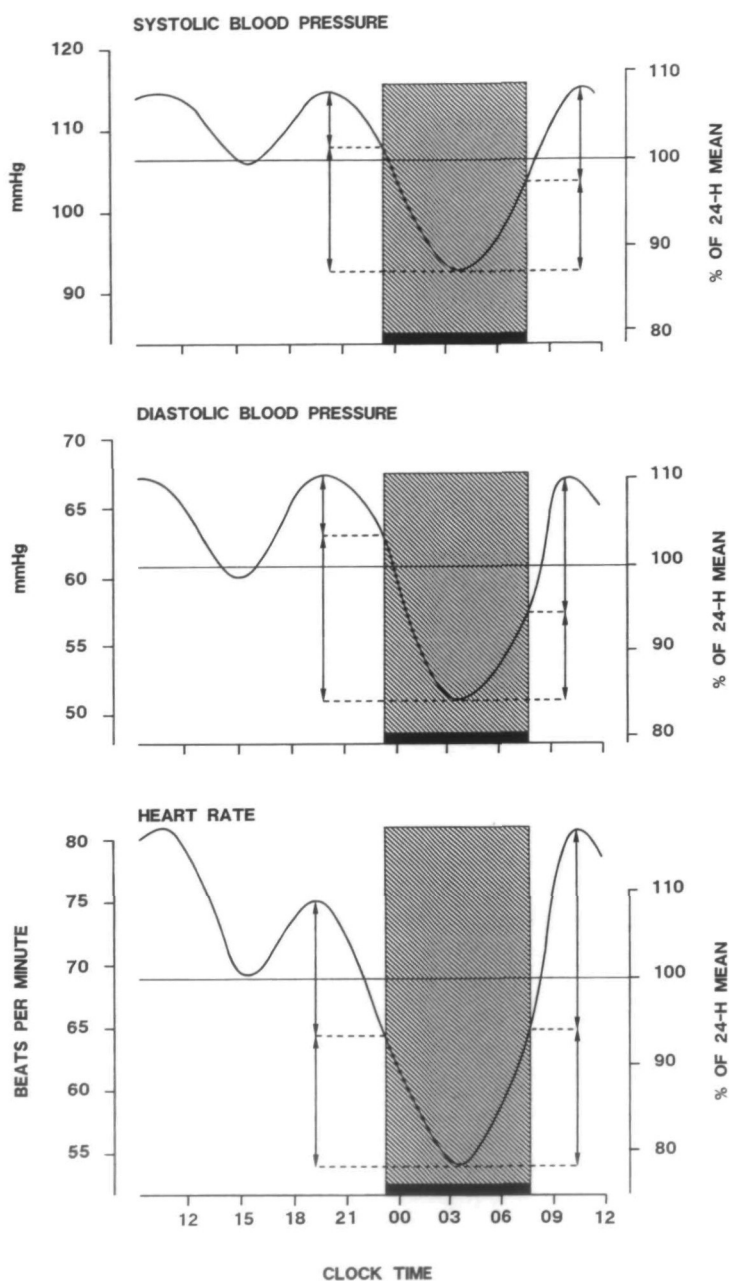


FIGURE 7. Schematic representation of the mean quantitative characteristics of the nycterohemeral systolic and diastolic blood pressures and heart rate variations illustrating contribution of sleep-wake/rest-activity cycle. Hatched areas indicate sleep periods derived from polygraphically recorded sleep. Horizontal lines drawn at 100% of the relative systolic and diastolic blood pressures and heart rate values represent mean 24-hour level for each measure.

with the Italian habit of "siesta," this nadir was also apparent in our study where recumbency and naps were not allowed during the daytime.

When the 24-hour variation is expressed in percentage of the 24-hour mean level, it appears that the amplitude is smallest for SBP, averaging only 11%, intermediate for DBP, averaging 14%, and largest for heart rate, averaging 20%. Thus, the detection of the 24-hour variations in blood pressure will generally be more reliable based on DBP rather than SBP. Studies that use the mean of systolic and diastolic measurements to characterize the 24-hour variation of blood pressure are thus more likely to fail to detect the rhythm or to underestimate its amplitude. The observation that heart rate undergoes a more pro-

found 24-hour variation than blood pressure is further supported by the visual inspection of the previously published patterns and in particular in patterns obtained using intra-arterial recordings, but this difference in relative amplitude of the blood pressure and heart rate rhythms was not discussed.<sup>27</sup>

Going to sleep lowered both blood pressure and heart rate. However, although falling asleep accounted for the greater part of the nocturnal decline in SBP and DBP (at least two thirds of the overall variation), it explained only 50% of the nocturnal decline in heart rate. Indeed, a significant decrease in heart rate before bedtime was demonstrated but declining trends in SBP and DBP before going to bed could not be documented. The lowering effect of

sleep on blood pressure and heart rate is a well-known phenomenon. Recently, Van den Meiracker et al<sup>8</sup> reported that the lowering effects of sleep on blood pressure and heart rate persist even when the subjects are restricted to bedrest during the entire 24-hour span. Interestingly, in this condition of uninterrupted recumbency, the overall amplitude of the 24-hour variation in blood pressure is reduced, but the amplitude of the rhythm in heart rate is unaffected, indicating that postural changes are not involved in causing the drop in heart rate immediately after bedtime.

The effects of morning awakening on SBP, DBP, and heart rate were similar, although more marked for heart rate. Before the end of sleep, a significant rise in SBP, DBP, and heart rate was already evident. Although still a matter of controversy,<sup>28</sup> the existence of a blood pressure rise during late sleep has been described by Miller-Craig et al<sup>5</sup> and, more recently, by Broadhurst et al.<sup>27</sup> As suggested by the results illustrated in Figure 6, this blood pressure rise in late sleep could be related to the well-known predominance of REM stages over slow wave stages as well as to a higher rate of occurrence of sleep interruptions.<sup>29</sup> Indeed, slow wave sleep has been associated with lower blood pressure levels, whereas REM sleep appeared characterized by more variability in blood pressure, resulting in higher mean blood pressure levels.<sup>30</sup>

The present findings, taken together with earlier observations, clearly indicate that the 24-hour variation in heart rate reflects modulatory influences that are different from those controlling nycterohemeral changes in blood pressure. Indeed, the schematic representations depicted in Figure 7 show that in the absence of a rest-activity cycle (i.e., if the subjects had remained awake and ambulatory throughout the 24-hour period), any residual 24-hour variation in SBP and DBP would have been of an amplitude too small to be detected. Thus, the 24-hour variation in blood pressure is primarily related to the rest-activity cycle. Because a blood pressure rhythm of reduced amplitude persists during continuous recumbency, the combined effects of postural changes and the wake-sleep transition appear to be the major factors responsible for the 24-hour rhythm in blood pressure. In contrast, even in the absence of a rest-activity cycle, our analysis indicates that a clear 24-hour rhythm in heart rate would still be apparent since the decline before bedtime would remain significant. Based on the findings of Van der Meiracker et al,<sup>8</sup> postural changes seem to have little effect on heart rate, and thus the nocturnal decline appears mainly caused by the sleep condition. Thus, the 24-hour rhythm of heart rate may reflect the existence of an endogenous circadian rhythm, amplified by the effects of sleep. Circadian variations of some plasmatic hormones such as atrial natriuretic peptide have been implicated in the 24-hour rhythmicity of heart rate.<sup>31</sup> Further studies will be necessary to delineate the mechanisms, endocrine or other, responsible for

causing the endogenous 24-hour periodicity of heart rate.

In conclusion, the present study provides a quantitative description of the 24-hour variations in blood pressure and heart rate in normal men and defines the relative contribution of the sleep-wake/rest-activity cycle to this variation. Because ambulatory blood pressure is currently considered to be the best predictor of target organ involvement, accurate definitions of its changes over the 24-hour cycle will be of crucial importance in relating specific abnormalities in the nycterohemeral pattern to hypertension and other cardiovascular diseases.

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KEY WORDS • blood pressure • heart rate • blood pressure monitoring • circadian rhythm • sleep