

# Continuous 24-Hour Assessment of the Neural Regulation of Systemic Arterial Pressure and RR Variabilities in Ambulant Subjects

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**In this study, we tested the hypothesis that the neural control of circulation in humans undergoes continuous but in part predictable changes throughout the day and night. Dynamic 24-hour recordings were obtained in two groups of ambulant subjects. In 18 hospitalized patients free to move, direct high-fidelity arterial pressures and electrocardiograms were recorded, and in an additional 28 nonhospitalized subjects, only electrocardiograms were obtained. Spectral analysis of systolic arterial pressure and of RR interval variabilities provided quantitative markers of sympathetic and vagal control of the sinus node and of sympathetic modulation of vasomotor tone. With this approach, the low-frequency (~0.1 Hz) component of RR interval and systolic arterial pressure variabilities is considered a marker primarily of sympathetic activity, whereas the high-frequency (~0.25 Hz) component of RR interval variability, related to respiration, seems to be a marker primarily of vagal activity. We observed a pronounced and consistent reduction in the markers of sympathetic activity and an increase in those of vagal activity during the night. In the invasive studies, while the subjects were still lying in bed after waking up, the markers of sympathetic activity rose rapidly and concomitantly with a simultaneous vagal withdrawal. Noninvasive studies confirmed the early morning rise of the markers of sympathetic activity and the circadian pattern of sympathovagal balance. These data indicate that the ominously increased rate of cardiovascular events in the morning hours may reflect the sudden rise of sympathetic activity and the reduction of vagal tone. (*Circulation* 1990;81:537-547)**

**T**he theoretical and practical importance of detecting a possible circadian variation of acute cardiovascular events has been appreciated for some time.<sup>1</sup> However, only recently have clinical studies been capable of indicating that the frequency of myocardial infarction,<sup>2</sup> sudden cardiac death,<sup>3,4</sup> transient myocardial ischemia,<sup>5,6</sup> and stroke<sup>7</sup> is not evenly distributed throughout the day and that the morning hours carry a greater risk. These epidemiologic findings, in addition, may provide some clue as to the pathogenetic and trigger mechanisms of

these cardiovascular events.<sup>1</sup> For instance, studies have reported that the clotting tendency of the blood appears elevated in the morning,<sup>8</sup> probably because of a lower fibrinolytic activity,<sup>9</sup> a greater platelet aggregability,<sup>10</sup> and a greater fibrinogen plasma concentration.<sup>11</sup> The circadian oscillation of all these variables participating in the coagulation system clearly indicates, on the one hand, the existence of some common mechanism of circadian oscillation and, on the other hand, suggests that this mechanism also serves as a trigger function.

Neural activities, at various levels of complexity, have furnished the most clear examples of circadian rhythms, the paradigm of which is the sleep-wakefulness cycle. It is well known that marked circulatory changes follow a similar circadian cycle and that they are likely to be mediated by neural adjustments.<sup>12,13</sup>

In this study, we addressed the problem of quantifying the circadian cycle of neural cardiovascular

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Received July 28, 1989; revision accepted October 4, 1989.

regulatory activities in free moving subjects. To this purpose, we applied a spectral analysis of RR interval and of systolic arterial pressure variabilities to the 24-hour ambulatory recordings of electrocardiograms and of direct high-fidelity measurements of arterial pressures.<sup>14</sup> Previous studies based on short-term analysis have already shown that this approach provides quantitative markers of sympathetic and vagal activities modulating the heart rate<sup>15</sup> and of the sympathetic activity regulating vasomotor tone.<sup>16</sup>

Results suggest that at about 6:00 AM, the pattern of neural cardiovascular control begins to undergo a drastic and rapid rearrangement characterized by a rise in sympathetic drive to the heart and blood vessels and a simultaneous reduction of vagal cardiac activity. We hypothesized that these rapid neural changes facilitate the higher rate of cardiovascular acute events occurring in the morning.

### Methods

#### *Invasive Studies*

Eighteen hospitalized patients (10 men and eight women; mean age,  $45 \pm 4$  years), with a history of episodic hypertensive crises or of stable hypertension, were used for this section of the study. They had no evidence of organic diseases. On the basis of intra-arterial pressure measurements, their pressure values ranged from normotension to hypertension. As part of a protocol prepared in accordance with institutional guidelines, these subjects underwent a 24-hour direct high-fidelity blood pressure recording<sup>14</sup> that used a miniature (diameter, 3F) catheter tip transducer (Millar, Houston, Texas), which was introduced into the radial artery of the nondominant arm by the Seldinger technique. The transducer has a high degree of constancy in gain and stability and also a wide band pass (better than 1 kHz); the pressure signal was recorded, along with the electrocardiogram, on a modified four-track Holter tape recorder (Remco, Milan, Italy). The signal was recorded with frequency modulation, and the frequency response of the entire record playback system had a  $-3$ -dB point at 50 Hz. To minimize tape-speed errors, a crystal-controlled 160-Hz signal was recorded on a channel of the portable recorder. This signal was used during playback by phase-locked loop circuitry (Remco), which provided an error signal proportional to any possible change in recording tape speed. This voltage was used to correct instantaneously the voltage supply of the DC motor of the playback unit, thus practically abolishing tape speed variations.

As part of the protocol, all subjects were woken at 6:00 AM. They were asked to remain in bed until 9:00 AM, at which time they were allowed to walk around the hospital. Furthermore, they were asked to perform light physical activity for a period of 2 hours, between 4:00 and 6:00 PM by walking in the hospital grounds. They all went to bed at approximately 10:00 PM. None of the subjects was receiving medication. All subjects gave informed consent to the study.

#### *Noninvasive Studies*

Twenty-eight healthy normotensive subjects (16 men and 12 women; mean age,  $37 \pm 2$  years), non-smokers ( $< 5$  cigarettes/day), and free of any sign of disease participated in this section of the study. None of these subjects was receiving medication. All subjects gave informed consent to the study.

The subjects were taken to the laboratory at about 11:00 AM and were connected to a two-channel Holter recorder (Remco), which was equipped with a tape-speed control device similar to that described previously for the invasive studies. Leads were modified X and Y. These subjects, being outpatients, were instructed to maintain a daily routine as close as possible to their normal one.

#### *Data Analysis*

Data were played back at 64 times real time. Analog-to-digital conversion was performed at 3,200 samples/sec for the arterial pressure recordings and at 19,200 samples/sec for the surface electrocardiogram to achieve a real-time analog-to-digital conversion of 50 and 300 samples/sec, respectively. Data was analyzed with a PDP 11/24 computer (Digital Equipment, Maynard, Massachusetts).

The principles of the software for data acquisition and spectral analysis have been described elsewhere.<sup>15,17,18</sup> Figure 1 depicts a schematic outline of the computer analysis of RR interval variability. From the surface electrocardiogram, the computer program calculated a series of 512 consecutive intervals as a function of beat numbers, thus obtaining the tachogram. A similar analysis was performed on systemic arterial pressure recordings, thus obtaining the series of systolic (systogram) and diastolic (diastogram) values.

From every series, simple statistics (mean and variance) and the autoregressive coefficients necessary to define the best estimate of the power spectral density were calculated. Every spectral component was identified by the center frequency and quantified by its power. The spectral power can be presented in absolute units and in a normalized form. With the methodology of this study, the oscillations with a frequency below 0.03 Hz cannot be properly described, hence oscillatory components between 0 and 0.03 Hz are considered to be DC noise.<sup>15</sup> These very low-frequency components can however be analyzed by different methodologies.<sup>19</sup> The oscillations with a center frequency at about 0.1 Hz (low frequency) and 0.25 Hz (high frequency) contain the major fraction of the information on neural modulation of the sinoatrial node and of arterial pressure (however, in the latter case, the high-frequency component is also largely affected by mechanical changes related to respiratory activity).<sup>16</sup>

It should be pointed out that, as mainly in the case of RR interval variability, if there are large variations in power among individual autospectra, the use of normalized units (NU) facilitates comparison among

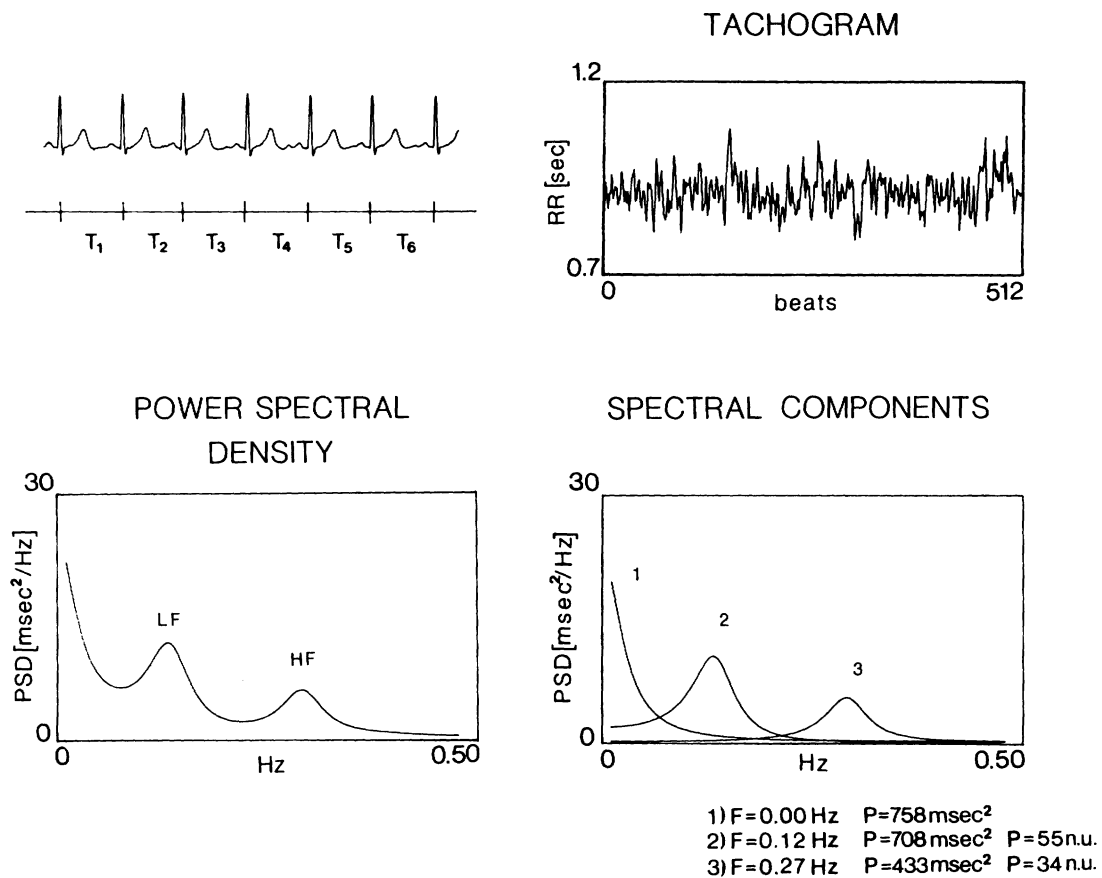


FIGURE 1. Schematic representation of the method used for the spectral analysis of RR interval variability. From the surface electrocardiogram (top left panel), the program computes the individual RR intervals ( $T_1$ - $T_6$ ) and stores them in memory as the tachogram. From the tachogram, the power spectral density estimate is computed. Two major components, low-frequency (LF) and high-frequency (HF), are usually recognized as well as a large and variable fraction of very slow oscillations (below 0.03 Hz), which are not considered in the analysis. Notice that the computer program automatically recognizes and prints out for each component the center frequency and associated power in absolute and normalized units (n.u.). Power spectral ordinates should be multiplied by  $10^3$ . PSD, Power spectral density.

different subjects or different conditions.<sup>15,20</sup> The normalization procedure consists of dividing the power of a given component by the total power minus the DC component.<sup>15</sup> Of importance, particularly in the case of RR interval variability, the relative ratio between the very low-frequency (“noise”) component and the remainder of the signal can vary considerably. For example, the ratio can vary from an ideal laboratory situation of resting conditions with a noise of approximately only 50% to dynamic conditions with a meaningful portion of the signal as low as about 15% of total variance.

In this study, we used a recursive version of the program,<sup>18,21</sup> which provided, depending on individual heart rate, more than 200 consecutive spectra for every subject during the 24-hour recordings.

**Statistics**

Data are presented as mean  $\pm$  SEM. Two-way analysis of variance with Scheffé’s test was used to assess differences among the four 6-hour periods during the day and to assess differences between subjects while

asleep, awake, or walking. Differences were considered significant at the 0.05 level.

**Results**

*Arterial Pressure and RR Interval Diurnal Variabilities in Hospitalized Patients*

In the group of 18 patients, who were hospitalized and free to move, arterial blood pressure showed the well-known day-night periodicity,<sup>12,13</sup> with greater values during the day and lower values during the night (Table 1 and Figures 2 and 3). The variance, that is, total variability, of systolic and diastolic arterial pressures underwent a circadian rhythm as well, with values lower during the night and higher during the day.

Spectral analysis of systolic and diastolic arterial pressure variabilities indicated that during the day the low-frequency ( $\sim 0.1$  Hz) component was greater than that during the night (Table 1 and Figures 2 and 3). Changes in the high-frequency ( $\sim 0.25$  Hz) component throughout the 24-hour period were less

**TABLE 1. The 24-Hour Spectral Analysis of Direct Systemic Arterial Pressure and RR Interval Variabilities in 18 Ambulant Hospitalized Subjects**

Time of day (hr)	Systolic arterial pressure		Low-frequency component		High-frequency component		
	Mean (mm Hg)	Variance (mm Hg <sup>2</sup> )	Power (mm Hg <sup>2</sup> /Hz)	Frequency (Hz)	Power (mm Hg <sup>2</sup> /Hz)	Frequency (Hz)	
12-6 PM	144±4	254±23	30.1±3.9	0.09±0.002	8.6±1.6	0.27±0.007	
6-12 PM	139±2	205±21	18.1±3.0	0.09±0.001	7.3±1.2	0.28±0.008	
0-6 AM	128±4*	191±24*†	7.1±1.6*†‡	0.09±0.002	9.2±3.4	0.28±0.008	
6-12 AM	130±4§	256±26	26.7±3.6	0.09±0.002	8.7±2.1	0.27±0.006	
Time of day (hr)	Diastolic arterial pressure		Low-frequency component		High-frequency component		
	Mean (mm Hg)	Variance (mm Hg <sup>2</sup> )	Power (mm Hg <sup>2</sup> /Hz)	Frequency (Hz)	Power (mm Hg <sup>2</sup> /Hz)	Frequency (Hz)	
12-6 PM	86±2	110±7	10.6±1.6	0.09±0.002	2.9±0.4	0.27±0.004	
6-12 PM	84±2	98±9	7.0±1.0	0.09±0.002	2.6±0.4	0.28±0.006	
0-6 AM	80±3	90±9†	4.7±1.0*†	0.09±0.002	2.0±0.4	0.28±0.007	
6-12 AM	86±3	118±10	9.9±1.8	0.09±0.002	3.0±0.6	0.28±0.005	
Time of day (hr)	RR interval		Low-frequency component		High-frequency component		Low/high frequency
	Mean (msec)	Variance (msec <sup>2</sup> )	Power (NU)	Frequency (Hz)	Power (NU)	Frequency (Hz)	
12-6 PM	685±25	7,327±701	57.3±2.3	0.10±0.002	16.9±1.6	0.28±0.007	4.4±0.4
6-12 PM	745±26	8,155±939	46.6±3.4	0.10±0.002	22.5±2.4	0.30±0.009	3.1±0.4
0-6 AM	845±37*†‡	9,993±560*†	35.8±2.7*†‡	0.10±0.002	30.7±3.5*†	0.30±0.010	1.6±0.2*†‡
6-12 AM	719±31	7,347±642	54.3±2.5	0.10±0.002	19.1±2.5	0.28±0.008	3.8±0.6

NU, normalized units.

\*0-6 AM vs. 12-6 PM; †0-6 AM vs. 6-12 AM; ‡0-6 AM vs. 6-12 PM; §6-12 AM vs. 12-6 PM; ||12-6 PM vs. 6-12 PM ( $p<0.05$ ).

evident (Table 1 and Figures 2 and 3). In more detail, systolic arterial pressure and its low-frequency component reached their minimal values during the night and started to rise in the morning, reaching their maximum values in just a few hours. These parameters leveled off in the early afternoon and increased again between 4:00 and 7:00 PM. The morning rise of the low-frequency component of systolic arterial pressure variability tended to be more rapid and to occur earlier than the rise in blood pressure itself as shown in Figures 2 and 3. In particular, for the grouped data, the low-frequency component rise started at 6:00 AM and peaked at 8:00 AM, thus corresponding to the period of time when the subjects were resting awake in bed. A clear increase in systolic arterial pressure was, instead, evident at about 10:00 AM and peaked at about 12:00 AM, corresponding to the period of light physical activity of the morning. Furthermore, a subsequent rise occurred in the afternoon (Figures 2 and 3) and peaked at about 5:00 PM, corresponding to the physical activity scheduled for the afternoon (see "Methods"). Table 2 shows that the last condition was associated with the highest values of arterial pressure and of the low-frequency component of systolic arterial pressure variability.

In this same group of subjects, the RR interval and its variability (Table 1) also showed a circadian pattern of changes. Maximal values of the RR interval occurred during the night, and minimal values occurred during the day; a prevailing low-frequency component occurred during the day, and a prevailing

high-frequency component occurred during the night. The changes in spectral components of RR interval and systolic arterial pressure variabilities occurred simultaneously.

#### *RR Interval Diurnal Variability in Nonhospitalized Subjects*

In the group of 28 normal nonhospitalized ambulant subjects, RR intervals had lower values during the day and higher values during the night. Table 3 indicates, furthermore, that this periodicity was similar to that observed in the group of hospitalized patients in whom direct arterial blood pressure recordings were also obtained.

Likewise, spectral analysis of RR interval variability confirmed the prevalence of the low-frequency component during the day as opposed to a prevailing high-frequency component during the night (Figures 4 and 5). Inspection of continuous (Figure 4) analysis of RR interval variability indicated large minute-to-minute changes in spectral components, the large day-night variations of which were also in apparent synchronism with the RR interval fluctuations.

The center frequency of the low- and high-frequency components underwent continuous changes at average values of  $0.10\pm 0.01$  and  $0.28\pm 0.02$  Hz, respectively (Figure 6). However, the frequency of the high-frequency respiratory component became very stable during the night, when the subjects on the basis of their diaries were sleeping (Figure 6).

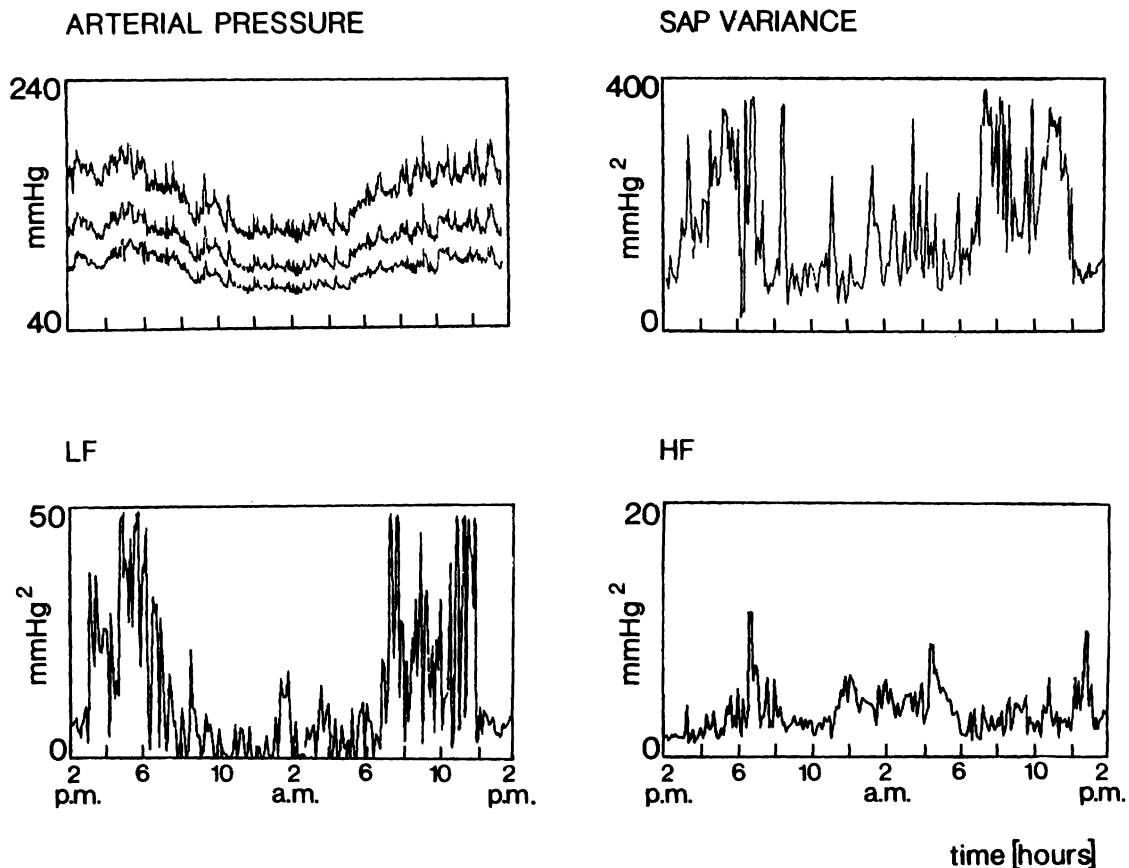


FIGURE 2. Computer analysis plots of the 24-hour high-fidelity arterial pressure variability in an ambulant hypertensive subject. Top left panel: Computer printout depicts systolic, diastolic, and integrated mean values of arterial pressure. Systolic arterial pressure (SAP) variance and its low- (LF) and high-frequency (HF) components are displayed in the other panels.

### Discussion

The neural control of the circulation has been traditionally explored mainly through the study of reflexes. However, in recent years, a new approach, based on the analysis of the short-term rhythmical oscillations of heart period and of arterial pressure, that is, an analysis in the frequency domain, seems to provide some additional information. In view of the relative novelty of the approach and of the technical differences characterizing the various attempts in this rapidly growing field, a few methodologic considerations seem appropriate before discussing the results of this study.

#### Power Spectral Analysis of Beat-to-Beat Variability of Cardiovascular Parameters

The general hypothesis behind this approach is that rhythms can be markers of functional states.<sup>15,21-23</sup> Since the initial studies, there has been general agreement on the concept that the power of high-frequency oscillations, which are related to respiration and correspond to the second-order rhythm, provides a marker of vagal activity.<sup>15,16,22,24,25</sup> The functional meaning of the oscillations occurring at a lower frequency, below approximately 0.15 Hz, was instead less clear. Initially, two bands of interest were

considered at about 0.09–0.15 and 0.02–0.09 Hz, which were interpreted as being mediated by both vagal and sympathetic activities.<sup>22</sup> More recently, however, interest has centered mostly on the 0.1-Hz component (low frequency), corresponding to the third-order rhythm.<sup>15,16,19,25</sup> The even lower oscillations, near 0 and below 0.03 Hz, cannot be properly analyzed with the algorithms used to quantify the other components and require a different methodology.<sup>19</sup> Accordingly, we considered the power of this component to be DC noise.<sup>15</sup>

The crucial point is that increasing evidence indicates that the low-frequency component is a marker of sympathetic activity because it is increased during tilt,<sup>15</sup> moderate physical exercise,<sup>18,26</sup> mental stress,<sup>27</sup> in several pathophysiologic states such as arterial hypertension<sup>28</sup> or after myocardial infarction,<sup>29</sup> and more importantly, in several well-reproducible experimental conditions leading to tonic increases in sympathetic efferent activity.<sup>16</sup>

Thus, the low- and high-frequency components and their ratio (i.e., low-frequency/high-frequency)<sup>15,21</sup> would provide a model to evaluate, though quite broadly, the dynamic changes of the sympathovagal balance. Some major differences, however, exist in the various methodologies most commonly used. The

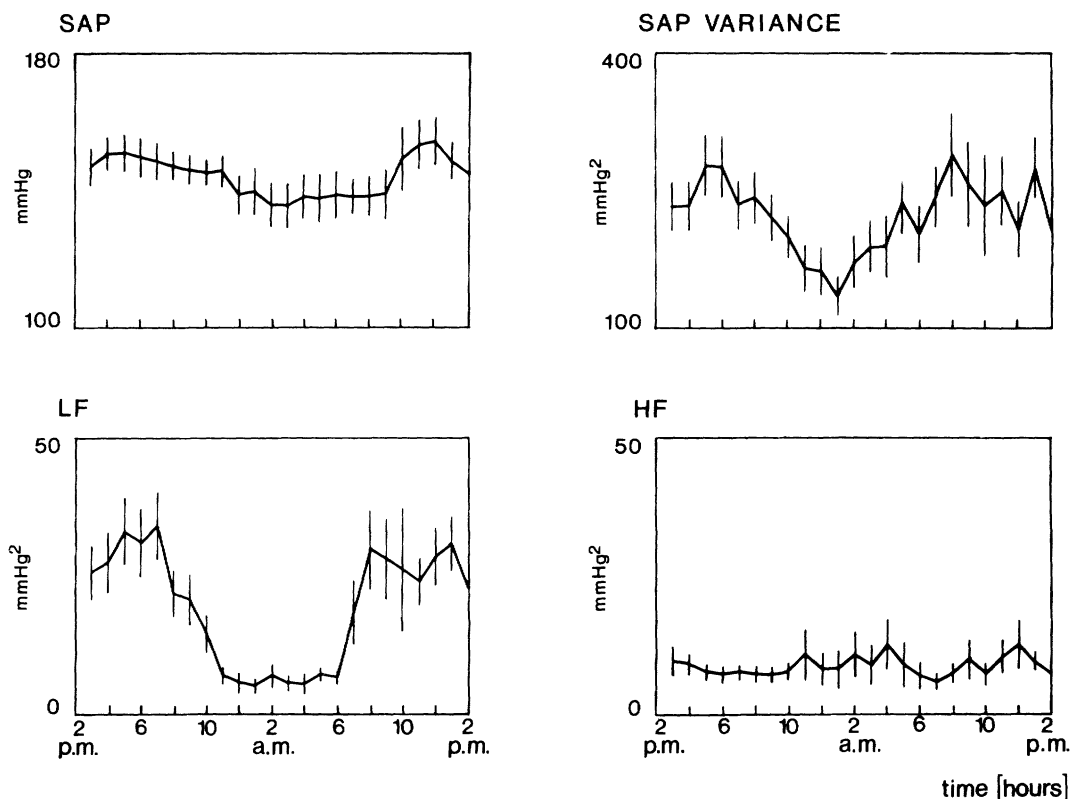


FIGURE 3. Plots of average hourly values of systolic arterial pressure (SAP), of its variance, and of low- (LF) and high-frequency (HF) components during 24 hours in a group of hospitalized patients free to move.

approach based on fast Fourier transform algorithms relies on the selection of predetermined bands of interest.<sup>22,25,30,31</sup> In addition, with the fast Fourier transform approach, all the power in the band of interest is considered, and no allowance is made to

clean the signal from possible contamination of very slow trends that would provide power mostly in the low-frequency end of the spectrum, thus increasing, for instance, the power of low-frequency by an unknown quantity.

TABLE 2. Spectral Analysis of Direct Systemic Arterial Pressure and RR Interval Variabilities in 18 Ambulant Hospitalized Subjects: Differences Between Periods of Sleep, Wakefulness, and Walking

	Systolic arterial pressure		Low-frequency component		High-frequency component		
	Mean (mm Hg)	Variance (mm Hg <sup>2</sup> )	Power (mm Hg <sup>2</sup> /Hz)	Frequency (Hz)	Power (mm Hg <sup>2</sup> /Hz)	Frequency (Hz)	
Sleep	128±4†	191±24	7.1±1.6*†	0.09±0.02	9.2±3.4	0.28±0.08	
Awake	139±7	256±46	30.1±6.4	0.08±0.002	7.3±1.8	0.27±0.01	
Walking	151±5	277±32	32.6±5.6	0.09±0.002	7.7±1.3	0.27±0.06	
	Diastolic arterial pressure		Low-frequency component		High-frequency component		
	Mean (mm Hg)	Variance (mm Hg <sup>2</sup> )	Power (mm Hg <sup>2</sup> /Hz)	Frequency (Hz)	Power (mm Hg <sup>2</sup> /Hz)	Frequency (Hz)	
Sleep	80±3	90±9	4.7±1.0	0.09±0.002	2.0±0.4	0.28±0.07	
Awake	77±4	130±14	11.3±3.3	0.09±0.004	2.5±0.4	0.27±0.09	
Walking	88±2	123±11	11.8±2.5	0.10±0.002	3.1±0.4	0.27±0.08	
	RR interval		Low-frequency component		High-frequency component		Low/high frequency
	RR (msec)	Variance (msec <sup>2</sup> )	Power (NU)	Frequency (Hz)	Power (NU)	Frequency (Hz)	
Sleep	845±37*†	9,993±560†	35.8±2.7*†	0.10±0.002	30.7±3.5*†	0.30±0.010	1.6±0.2*†
Awake	714±41	7,755±1185	53.7±4.2‡	0.10±0.003	16.3±2.3	0.29±0.014	4.6±1.2
Walking	668±24	6,788±735	64.5±2.8	0.10±0.003	14.5±1.9	0.28±0.010	5.6±0.7

NU, normalized units.

\*Sleep vs. awake, †sleep vs. walking, ‡awake vs. walking; *p*<0.05.

TABLE 3. The 24-Hour Spectral Analysis of RR Interval Variability in 28 Ambulant Normotensive Subjects

Time of day (hr)	RR interval		Low-frequency component		High-frequency component		Low/high frequency
	Mean (msec)	Variance (msec <sup>2</sup> )	Power (NU)	Frequency (Hz)	Power (NU)	Frequency (Hz)	
12-6 PM	688±14	19,181±2,295	59.74±3.06	0.11±0.02	16.72±1.05	0.28±0.03	8.52±1.16
6-12 PM	763±19	21,448±2,810	57.16±2.70	0.10±0.02	19.12±0.99	0.29±0.03	6.90±1.14
0-6 AM	966±28*†‡	27,452±3,667	45.48±2.10*†‡	0.09±0.02	30.69±1.60*†‡	0.27±0.04	2.41±0.26*†‡
6-12 AM	753±19§	24,186±3,172	57.67±2.84	0.10±0.02	21.09±1.75	0.28±0.03	6.80±0.86

NU, normalized units.

\*0-6 AM vs. 12-6 PM; †0-6 AM vs. 6-12 AM; ‡0-6 AM vs. 6-12 PM; §6-12 AM vs. 12-6 PM; ||12-6 PM vs. 6-12 PM; p<0.05.

The approach based on the autoregressive algorithms, as in this study, does not require the use of predetermined bands of interest, but on the contrary, it is capable of providing information on the number, power, and center frequency of any statistically significant spectral component<sup>15,16</sup> (for more details, see References 15 and 32). This feature allows the subtraction of the DC noise (i.e., very low-frequency trends) and also the use of normalization procedures,<sup>15,20</sup> which is important to facilitate comparisons among different spectra when there are large differences in total power, that is, variance, or in DC noise. The latter is particularly important in dynamic conditions in which the power associated to that component can vary consider-

ably (see "Methods"). The normalization procedure used in our study accounts for changes in total power and in DC component. At any rate, the changes in spectral components are directionally similar when evaluated in normalized or absolute units.<sup>16</sup>

With regard to the use of the low-frequency component of arterial pressure as an indicator of sympathetic vasomotor tone,<sup>16</sup> it should be stressed that in dynamic conditions a high-fidelity recording<sup>14</sup> seems necessary to collect data that do not require visual editing. In fact, a fluid-filled catheter-manometer system could not avoid motion artifacts and an unpredictable deterioration of waveforms resulting in a deformation of the variability signal.<sup>33</sup>

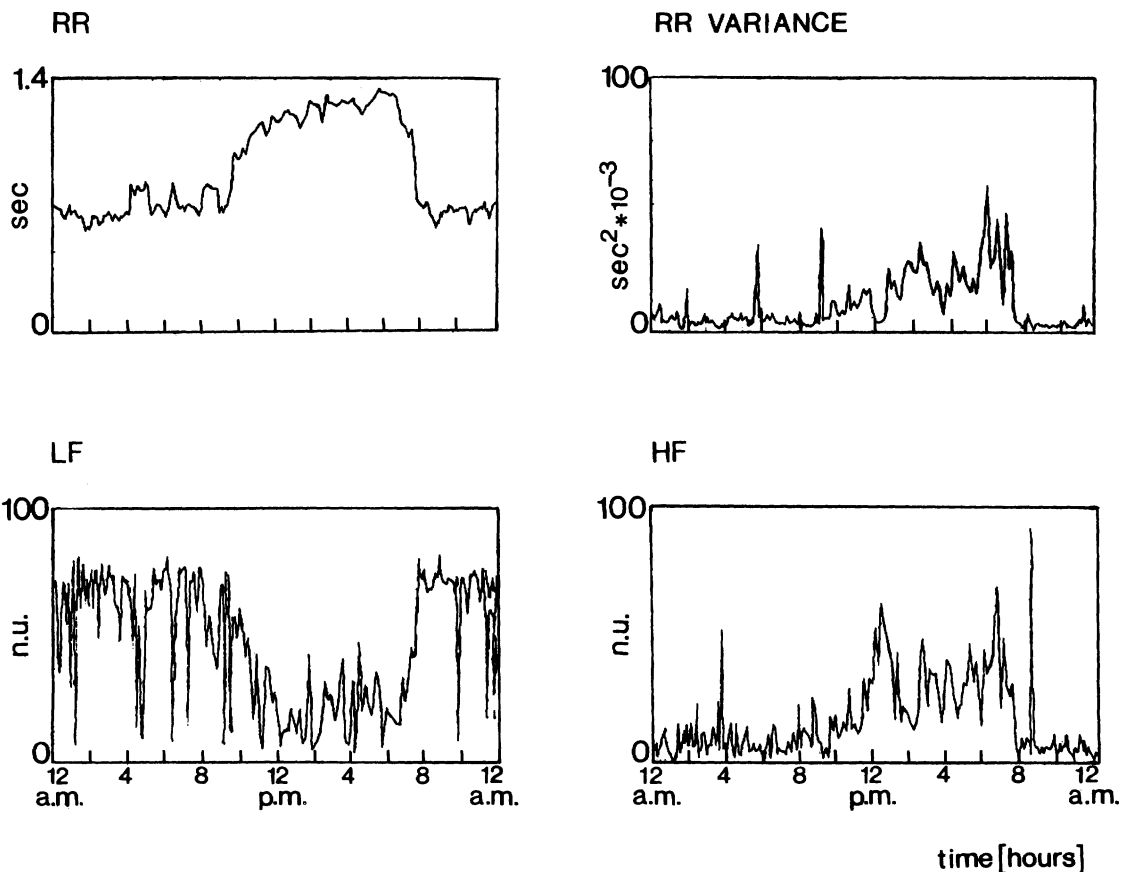


FIGURE 4. Computer analysis plots of 24-hour RR interval variability in a nonhospitalized normotensive subject. RR interval values, RR interval variance (in absolute units), and the low- (LF) and high-frequency (HF) components (in normalized units) are represented.

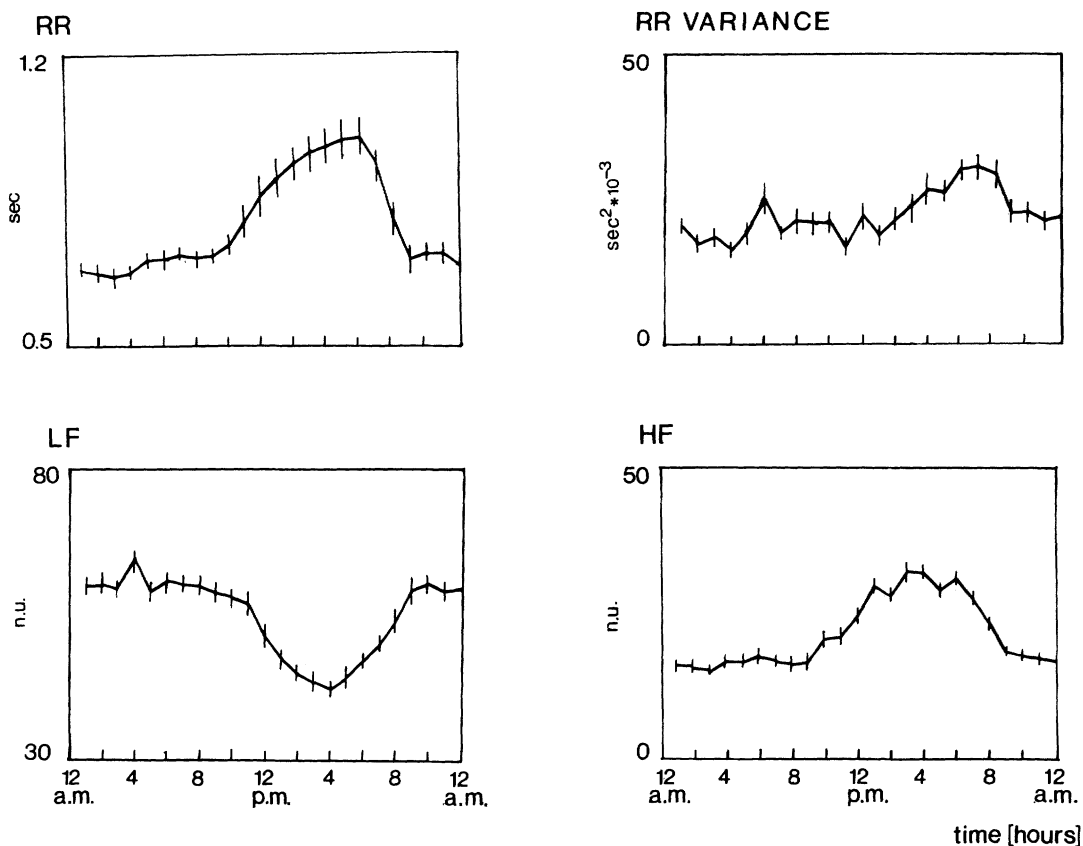


FIGURE 5. Plots of average hourly values of RR interval, of its variance (in absolute units), and of low- (LF) and high-frequency (HF) components (in normalized units) during 24 hours in a group of nonhospitalized subjects free to move.

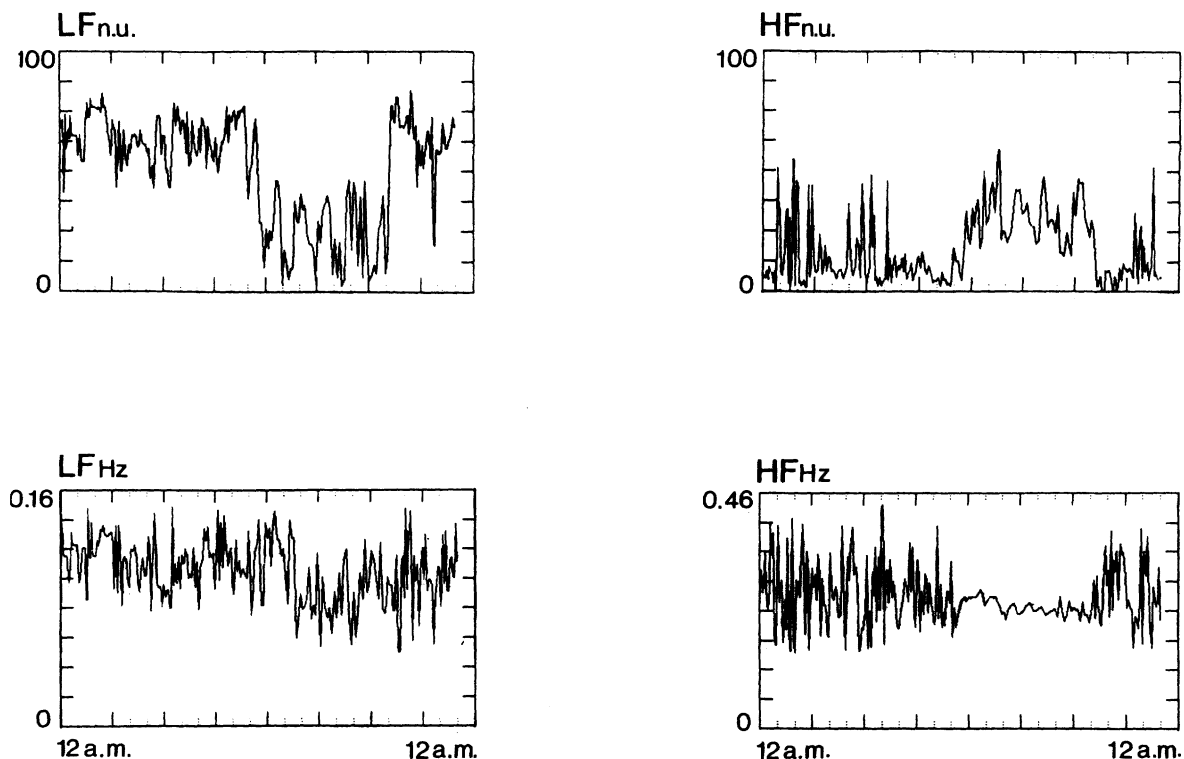


FIGURE 6. Computer analysis plots of continuous 24-hour changes in power (top panels) and center frequency (bottom panels) of low- (LF) and high-frequency (HF) components of RR interval variability in a normotensive subject free to move.

### *Circadian Variations in Markers of Sympathovagal Interaction*

In this study, we examined two groups of ambulant subjects: one group of hospitalized patients in whom high-fidelity arterial pressure and electrocardiograms were recorded for 24 hours, and a second group of outpatients, who were free to follow their normal daily activity and in whom only the electrocardiogram was recorded. The main finding in both groups was that the markers of sympathetic and vagal regulation of heart rate underwent day-night changes,<sup>21,34</sup> characterized by sympathetic predominance during the day and vagal predominance during the night.

Concerning the timing of controlled daily activity of the hospitalized patients, all were in bed by approximately 10:00 PM, were awake by 6:00 AM, and remained alert in bed until 9:00 AM. Subsequently, they got out of bed and started the minimal activity of morning toilet; in the afternoon between 4:00 and 6:00 PM, they performed a period of light physical activity.

The marker of sympathetic tone, that is, the low-frequency component, was minimal at night and began to rise at approximately 6:00 AM, as assessed by both RR interval and systolic arterial pressure variabilities. Arterial pressure started to increase somewhat later, at the moment when the subjects got out of bed. This finding may be interpreted assuming that physical activity, and not arousal per se, is a major determinant of the morning rise in arterial pressure. This is in keeping with the observation that the maximal values of arterial pressure were observed during the period of scheduled physical activity in the afternoon. Furthermore, as we have already described,<sup>15,26</sup> tilt induces a marked rise in the low-frequency component of arterial pressure variability with little change in pressure, whereas no further increase in the low-frequency component was observed with treadmill exercise,<sup>26</sup> which was accompanied, instead, by a marked rise in arterial pressure. Taken together, these observations support the concept that the mechanisms controlling arterial pressure and its variability are partially independent.<sup>35</sup> However, light physical exercise may represent a moment of higher sympathetic drive compared with morning waking as suggested by the observation that the low-frequency component of RR interval variability was also higher during walking. This indicates, in our opinion, the importance of using as many markers as possible to improve the highly indirect definition<sup>24,36</sup> of sympathetic or vagal tone.

Another important aspect of this study is the observation that the circadian changes in sympathovagal balance of heart rate regulation assessed with RR interval variability were surprisingly similar in a population of hospitalized subjects, whose daily routine was relatively standard, and in nonhospitalized subjects, whose daily routine was varied much more.

The changes in the high-frequency component of RR interval variability appeared to be directionally similar to those in total variance and to be the

reciprocal of those occurring in the low-frequency component. On the other hand, the rise in the low-frequency component of RR interval variability appeared much faster in individual subjects than in the grouped data (compare Figures 4 and 5), possibly as a reflection of dispersal due to desynchronization of daily activities.<sup>1</sup>

As a final point, it is worth observing that the slow day-night changes in sympathetic and vagal markers showed also fast variations, a characteristic that is also peculiar to the gain of the RR interval and systolic arterial pressure relation when this is continuously assessed with cross-spectral analysis of arterial pressure and heart period throughout the 24 hours.<sup>18</sup> Such fast changes, indicating a permanent dynamic interaction, were also clearly evident in the graphic analysis of the center frequencies of both low- and high-frequency components, an analysis that can be performed with our methodology. However, of interest, the high-frequency center frequency underwent a clear period of stability that, on the basis of reported behavior and diary, was likely to correspond to sleep.

### *Clinical Implications*

This investigation describing the reciprocal relation characterizing the sympathovagal balance throughout the day supports the interpretation of previous large scale clinical studies that among patients recovering from myocardial infarction those with a lower heart rate variability had a greater mortality.<sup>37</sup> A detailed subsequent analysis indicated that a lower heart rate variability was accompanied by a higher average day-night heart rate and by a smaller day-night difference; in parallel, the number of consecutive RR intervals differing by more than 50 msec and the number of short bursts of changes in cycle length were less numerous.<sup>38</sup> All these data were interpreted as suggesting a lower parasympathetic and higher sympathetic tone.

The results of this study may also be relevant to the recent clinical observations that a variety of acute cardiovascular events, namely myocardial infarction,<sup>2</sup> sudden death,<sup>3,4</sup> transient myocardial ischemia<sup>5</sup> accompanied with or without pain,<sup>39</sup> arrhythmias,<sup>40,41</sup> and cerebrovascular events,<sup>7</sup> all showed a significant rise in frequency in the early morning hours and an additional period of increased frequency in the afternoon. The continuous assessment of spectral markers of neural cardiovascular regulation indicated a well-defined pattern of changes in the sympathovagal balance, as inferred from heart period and arterial pressure variabilities. The sudden morning rise in sympathetic tone could well be the physiologic trigger<sup>1</sup> initiating a complex cascade of events that, in the presence of suitable pathophysiologic conditions, leads to an acute cardiovascular event.

In conclusion, the present approach in the frequency domain, though providing only broad markers of neural regulation, corresponds to the first possibility reached so far to continuously monitor the dynamic changes of the sympathovagal balance.

**Acknowledgment**

We thank Ms. Y. Stewart for typing the manuscript.

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KEY WORDS • high-fidelity dynamic arterial pressure recording • sympathetic activity • vagal activity • power spectrum • blood pressure