

# Baroreflex Buffering of Sympathetic Activation During Sleep

## Evidence From Autonomic Assessment of Sleep Macroarchitecture and Microarchitecture

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**Abstract**—We examined the effects of sleep microstructure, ie, the cyclic alternating pattern (CAP), on heart rate (HR)- and blood pressure (BP)-regulating mechanisms and on baroreflex control of HR in healthy humans and tested the hypothesis that sympathetic activation occurring in CAP epochs during non-rapid eye movement (non-REM) sleep periods is buffered by the arterial baroreflex. Ten healthy males underwent polysomnography and simultaneous recording of BP, ECG, and respiration. Baroreflex sensitivity (BRS) was calculated by the sequences method. Autoregressive power spectral analysis was used to investigate R-R interval (RRI) and BP variabilities. During overall non-REM sleep, BP decreased and RRI increased in comparison to wakefulness, with concomitant decreases in low-frequency RRI and BP oscillations and increases in high-frequency RRI oscillations. These changes were reversed during REM to wakefulness levels, with the exception of RRI. During CAP, BP increased significantly in comparison to non-CAP and did not differ from REM and wakefulness. The low-frequency component of BP variability was significantly higher during CAP than non-CAP. RRI and its low-frequency spectral component did not differ between CAP and non-CAP. BRS significantly increased during CAP in comparison to non-CAP. BRS was not different during CAP and REM and was greater during both in comparison with the awake state. Even during sleep stages, like non-REM sleep, characterized by an overall vagal predominance, phases of sustained sympathetic activation do occur that resemble that occurring during REM. Throughout the overnight sleep period, the arterial baroreflex acts to buffer surges of sympathetic activation by means of rapid changes in cardiac vagal circuits. (*Hypertension*. 2004;43:814-819.)

**Key Words:** sympathetic nervous system ■ baroreflex ■ heart rate ■ blood pressure

Growing evidence indicates that sleep is not devoid of cardiovascular risk.<sup>1,2</sup> The mechanisms linking sleep to cardiovascular events are not clearly defined, yet the most likely contributor appears to be the autonomic nervous system.<sup>1,2</sup> Specifically, the increase in sympathetic activity occurring during rapid eye movement (REM) sleep has been invoked as a potential trigger for nocturnal arrhythmias in this period and for the higher-than-expected incidence of cardiovascular events in the early morning hours after awakening.<sup>1-5</sup> However, Lavery et al<sup>2</sup> have clearly shown that a considerable rate of cardiovascular events occur throughout the overnight period. It thus appears that the adverse consequences of sleep may not be limited to the REM phase.

Concerning the autonomic modulation of the cardiovascular system, the general view is that compared with wakefulness, light and deep sleep (non-REM) is characterized by a vagal predominance, as opposed to the sympathetic predom-

inance of REM.<sup>5-7</sup> Studies investigating sleep structure have led to the identification of a natural electroencephalographic arousal rhythm within the non-REM sleep stages, related to transient lightnings of sleep depth, known as the cyclic alternating pattern (CAP).<sup>8,9</sup> CAP corresponds to a prolonged oscillation of the arousal level, whereas the complementary condition, non-CAP (NCAP), is closely related to a degree of stability in sleep depth.<sup>8,9</sup> Functionally, CAP translates a condition of sustained arousal instability; however, the arousal swings that characterize CAP sequences are not driven by any motor or respiratory disturbances and are associated with variations of autonomic activity.<sup>8,9</sup> Spectral analysis studies reported an increase in the low-frequency (LF) and a decrease in the high-frequency (HF) component of heart rate variability (HRV) during CAP compared with non-CAP sequences,<sup>10,11</sup> suggesting the occurrence of nighttime periods of relative sympathetic activation even during

Received December 22, 2003; first decision January 7, 2004; revision accepted January 29, 2004.

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*Hypertension* is available at <http://www.hypertensionaha.org>

DOI: 10.1161/01.HYP.0000121364.74439.6a

phases, like non-REM sleep, characterized by an increase in the background level of parasympathetic activity. These findings would indicate that surges of sympathetic activity may occur not only during REM. They also suggest the need to take into consideration sleep microstructure when evaluating the effect of sleep on cardiovascular autonomic regulation. Studies performed so far on sleep microstructure dealt with HRV only. However, neural cardiovascular regulation is rather complex and made of several intertwined mechanisms that involve the control of HR and blood pressure (BP) and the relationship between changes in BP and HR through the arterial baroreflexes. No one study has addressed the influences of sleep microstructure on the arterial baroreflex control of HR, which is a key component of cardiovascular homeostasis and carries relevant pathophysiological and prognostic information.<sup>12</sup> A more thorough understanding of sleep microarchitecture-related neural regulation has important clinical implications, because it may help to clarify why some cardiovascular events often occur at night.

Accordingly, in this study, we examined the effects of sleep macrostructure and microstructure on HR- and BP-regulating mechanisms and on baroreflex control of HR in healthy humans and tested the hypothesis that the arterial baroreflex acts to buffer sympathetic activations occurring during the overnight period.

## Methods

### Subjects

The study was conducted on 10 healthy men subjects (aged  $26.5 \pm 4.2$  years). All subjects were nonsmokers and were using no medications. Subjects were asked to avoid caffeine, alcohol, and physical exertion for 24 hours before the study. No one had history of sleep disorders. At the time of admission to the study, all subjects underwent a physical examination and routine laboratory test. All gave informed consent. The study has been approved by the Institutional Ethical Committee.

### Recorded Variables

Subjects were connected to an analogical multichannel signal conditioner and amplifier/filter (Marazza, Monza, Italy). The electrocardiographic signal was recorded from a precordial chest lead. BP was continuously and noninvasively measured by Finapres (Ohmeda 2300). The cuffed finger was maintained at heart level with the aid of sandbags and an arm board. Respiratory signal was recorded by means of a piezoelectric thoracic belt. The analogical signals were sampled at 300 Hz per channel and stored on the hard disk for subsequent analyses.

### Sleep Recordings

Polysomnographic recordings were performed with a computerized EEG system (Stellate System; Westmount, Quebec, Canada). Montage included 2 EEG (C3-A2, O2-A1), 2 electrooculographic (ROC-A1, LOC-A1), and 3 EMG channels (mylohyoideus and anterior tibialis muscles). Electrodes were positioned according to the International 10 to 20 System.

### Experimental Protocol

All-night polysomnographic studies were performed after 1 night of habituation to the laboratory environment. The instrumentation started, on average, at 11:00 PM. Analyses were performed on the signals recorded during the awake state in the immediate pre-sleep period with the subjects resting supine (10 minutes) and on data segments recorded during light sleep (stage II [S2]), deep sleep (stage III-IV, slow-wave sleep [SWS]), and REM sleep. Sleep was

staged according to the criteria of Rechtschaffen and Kales.<sup>13</sup> Subsequently, CAP and NCAP sequences were detected in each recording during S2 and SWS, according to the rules defined by Terzano et al.<sup>9</sup> We studied 3 different epochs of at least 5 minutes from CAP and 3 different epochs from NCAP periods during both S2 and SWS.<sup>11</sup> For each subject, 12 epochs were selected (3 from S2-CAP, 3 from S2-NCAP, 3 from SWS-CAP, and 3 from SWS-NCAP).<sup>11</sup> To avoid gross effects on R-R interval (RRI) and BP variability, only CAP and NCAP periods without arousals were selected.

### Spontaneous Baroreflex Analysis

Details of this analysis have been previously described.<sup>14,15</sup> Briefly, the mean slope of spontaneous sequences of consecutive beats characterized by systolic blood pressure (SBP) and RRI changing in the same direction (either increasing, ie, up-sequences or decreasing, ie, down-sequences) was calculated and taken as a measure of the integrated baroreflex sensitivity (BRS).<sup>16</sup>

### Power Spectral Analysis

The methodology for autoregressive power spectral analysis of RRI and finger SBP variabilities has been described previously.<sup>17-19</sup> Spectral analysis of respiratory activity was performed only to assess the main respiratory frequency.<sup>17-19</sup> Two main components were considered in the RRI and SBP variability signals: that in the frequency band from 0.04 to 0.15 Hz (low-frequency [LF]) and that in the range from 0.15 to 0.4 Hz (high-frequency [HF]). The power density of each spectral component was calculated in absolute values and normalized units (nu).<sup>17,20</sup> The normalized LF component of RRI ( $LF_{RR}$ ) and the absolute LF component of BP ( $LF_{BP}$ ) variability are considered markers of sympathetic cardiac and vascular modulation, respectively, whereas the normalized HF component of RRI variability would reflect respiratory-driven vagal modulation to the sinoatrial node.<sup>17,19-22</sup> Accordingly, spectral power of RRI variability will be presented only in normalized units.

### Statistical Analysis

Comparisons among the awake state and the different sleep stages were performed by the Friedman ANOVA on ranks. Pairwise multiple comparison procedures were performed by the Student-Newman-Keuls test. Differences were considered statistically significant at  $P < 0.05$ .

## Results

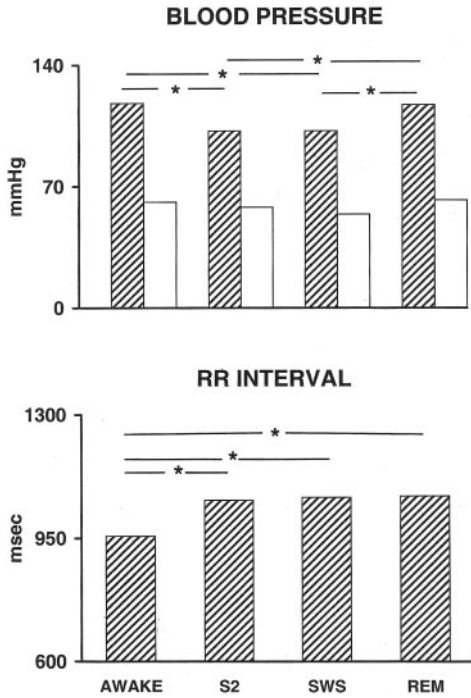
Sleep characteristics are reported in Table 1. A normal sleep macrostructure was observed in all subjects. SBP decreased during S2 and SWS as compared with during wakefulness, whereas it recovered back to wakefulness during REM (Figure 1). Diastolic BP did not show significant changes during the different sleep stages. As compared with wakefulness, RRI increased significantly during sleep without differences among S2, SWS, and REM (Figure 1).

The relative bradycardia was accompanied by a progressive increase in the normalized  $HF_{RR}$  with increasing sleep depth from wakefulness to SWS followed by a decrease to the

**TABLE 1. Sleep Characteristics (means  $\pm$  SD)**

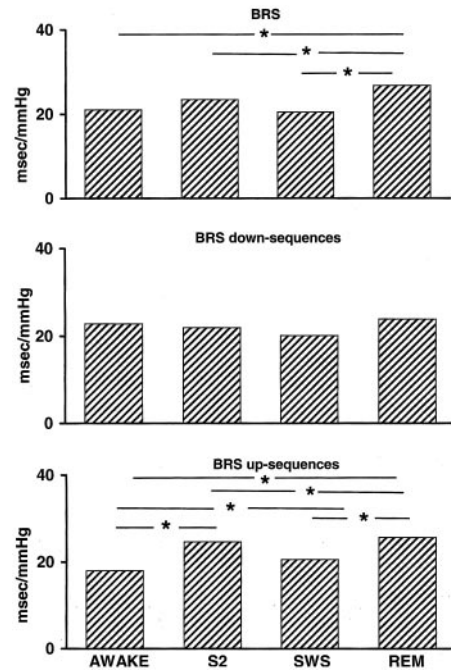
Total Sleep Time (min)	396 $\pm$ 38.0
Stage I, %	10.6 $\pm$ 2.8
Stage II, %	53.2 $\pm$ 8.9
Stage III-IV, %	16.5 $\pm$ 3.9
REM, %	16.8 $\pm$ 4.1
Awakening, %	3.9 $\pm$ 2.4

REM indicates rapid eye movement.



**Figure 1.** Systolic (SAP, hatched bars) and diastolic (DAP, open bars) blood pressure (upper panel) and R-R interval (bottom panel) during sleep. S2 indicates light sleep; SWS, slow-wave sleep; REM, rapid eye movement sleep. \* $P < 0.05$  among sleep stages by ANOVA on ranks.

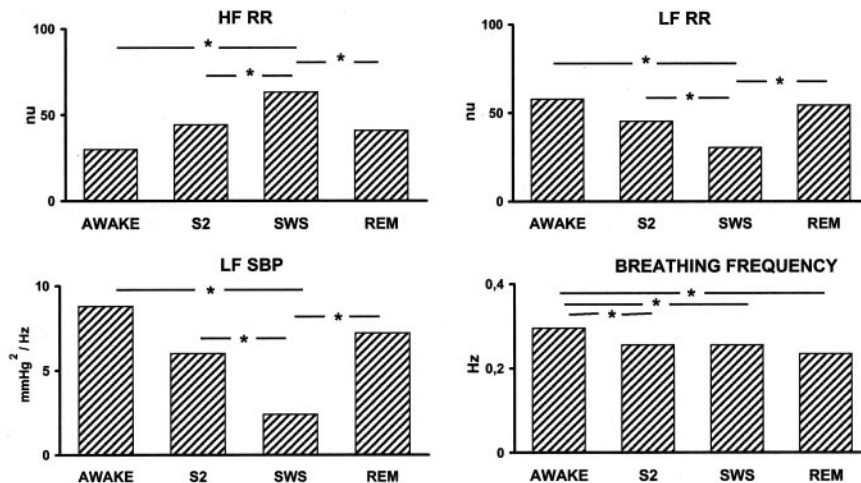
wakening level during REM. Normalized  $LF_{RR}$  showed a significant decrease from wakefulness as sleep deepened, followed by a significant increase during REM to the level observed during the awake state (Figure 2).  $LF_{SBP}$  decreased significantly during SWS compared with the awake state, and then it markedly and significantly increased to the waking level during REM (Figure 2). Respiratory frequency decreased slightly, albeit significantly, during sleep, without differences between the different sleep stages (Figure 2). BRS, as estimated by pooling together both up-sequence and down-sequences, showed an increase from wakefulness to sleep, which attained a statistical significance only during REM. However, when we analyzed separately up-sequences



**Figure 3.** Baroreflex sensitivity (BRS) for up-sequences and down-sequences pooled together (upper panel) and for down-sequences (middle panel) and up-sequences, (bottom panels) during the different sleep stages. \* $P < 0.05$  among sleep stages by ANOVA on ranks.

and down-sequences, we found that baroreflex gain increased significantly in response to loading stimuli, ie, increasing BP ramps, during all sleep stages as compared with wakefulness, attaining the maximum value during REM, whereas it did not differ significantly in response to unloading stimuli, ie, decreasing BP ramps, during sleep as compared with wakefulness (Figure 3).

The results of the comparison of the cardiovascular variables and autonomic indexes according to sleep microstructure analysis are shown in Table 2 and Figure 4. RRI was not significantly different between CAP and non-CAP conditions, whereas SBP was significantly higher during CAP SWS than non-CAP SWS. BP values during CAP conditions were not significantly different from those recorded during



**Figure 2.** High-frequency ( $HF_{RR}$ , left upper panel) and low-frequency ( $LF_{RR}$ , right upper panel) components of R-R interval variability, low-frequency component of SBP variability ( $LF_{SBP}$ , left bottom panel), and breathing frequency (right, bottom panel) during the different sleep stages. \* $P < 0.05$  among sleep stages by ANOVA on ranks.

**TABLE 2. Spectrum Analysis of R-R Interval and Systolic Arterial Pressure Variability and Spontaneous Baroreflex Sensitivity During Sleep**

Variables	Awake	Non-CAP S2	CAP S2	Non-CAP SWS	CAP SWS	REM	P (ANOVA)	Multiple Comparison
R-R interval, ms	956.0	1031.5	1083.5	1067.0	1084.5	1070.5	0.002	*†‡
Variance, ms <sup>2</sup>	4367.5	5262.0	4520.5	3243.0	2692.0	15935.0	0.001	‡¶
Low frequency, nu	57.7	43.9	41.9	36.7	33.9	54.4	0.004	*†¶
High frequency, nu	29.9	47.9	53.5	55.5	59.7	40.9	0.001	*†§¶
SBP, mm Hg	118	107	108	102	110.5	117	0.007	*†§
Variance, mm Hg <sup>2</sup>	23.9	20.1	24.1	14.7	15.3	35.9	0.06	
Low frequency, mm Hg <sup>2</sup> /Hz	8.8	4.2	6.3	2.6	3.5	7.2	0.001	*†§¶
BRS, ms/mm Hg	21	24.9	27**	20.5	24.8	26.7††	0.001	*†‡§
BRS up, ms/mm Hg	18	24	30.2	20.8	26.5	25.6	0.001	†‡§
BRS down, ms/mm Hg	22.8	25.7	24.8	20.3	22.9	23.8	0.25	
Baroreflex sequences, n	67.3	31.2	52.2	37.5	50.0	89.9	0.001	*¶
Respiration, Hz	0.29	0.26	0.26	0.27	0.27	0.24	0.001	*†‡

Data are given as median values through ANOVA on ranks.

nu indicates normalized units; SBP, systolic blood pressure; BRS, average baroreflex sensitivity; BRS up, baroreflex sensitivity for up-sequences; BRS down, baroreflex sensitivity for down-sequences. All other abbreviations are as defined in the text.

Symbols indicate between-condition differences as follows: \*Awake vs non-CAP; †Awake vs CAP; ‡Awake vs REM; §CAP vs non-CAP; ¶CAP vs REM; ||Non-CAP vs REM; \*\*Not significant vs non-CAP S2; ††Not significant vs non-CAP S2.

REM.  $LF_{SBP}$  was significantly higher during CAP than non-CAP conditions during both S2 and SWS, although it was less than during REM.  $LF_{RR}$  (nu) was not significantly different between CAP and non-CAP epochs during both S2 and SWS. HF was significantly higher and LF significantly lower in both non-CAP and CAP than in REM. BRS showed a trend toward an increase from awake to non-CAP, CAP, and REM sleep. When up-sequences and down-sequences were analyzed separately, BRS in response to increasing BP ramps was significantly greater during CAP than non-CAP during both S2 and SWS, and not different between CAP and REM. Again, no significant differences were detected in BRS in

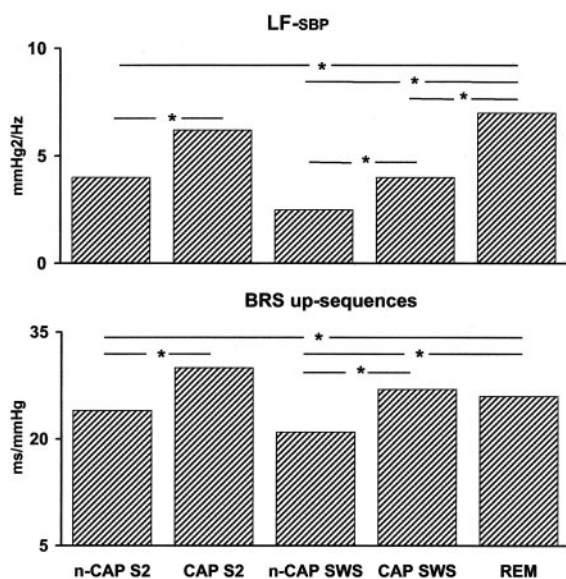
response to decreasing BP ramps during sleep as compared with wakefulness and among the different sleep epochs (Table 2).

## Discussion

The novel findings ensued from the analysis of sleep microstructure and macrostructure are: (1) that even during sleep stages characterized by an overall vagal predominance, phases of sustained sympathetic activation do occur that resemble that occurring during REM; (2) that throughout the overnight asleep period, the arterial baroreflex acts to buffer surges of sympathetic activation by means of rapid changes in cardiac vagal circuits.

Previous studies dealing with sleep-related neural cardiovascular regulation<sup>5-7,23-25</sup> have focused on the conventional scoring defining the sleep macrostructure.<sup>1,3</sup> As in these studies, we observed a decrease in BP during S2 and SWS, with a recovery to the awake level during REM associated with parallel changes in  $LF_{SBP}$ . HR decreased throughout the sleep period in comparison with wakefulness, and this decrease was associated with increases in the HF and decreases in the LF component of HRV during S2 and SWS, which were reversed during REM. This overall picture points to a cardiac parasympathetic predominance during non-REM and to a peripheral sympathetic activation during REM, in agreement with studies that directly recorded peripheral sympathetic nerve traffic.<sup>5-7</sup> The lack of a tachycardic effect, despite the simultaneous increase sympathetic activation, frequently reported during REM<sup>5,6,24,25</sup> could be explained through a vagally mediated baroreflex mechanism offsetting cardiac sympathetic activation, as suggested by the increase in BRS in response to hypertensive stimuli.<sup>25</sup>

As to the lack of significant changes in BRS down-sequences, a different buffering effect of arterial baroreflex in response to increases and decreases in BP during sleep has



**Figure 4.** Low-frequency component of SBP variability ( $LF_{SBP}$ , upper panel) and baroreflex sensitivity (BRS) for up-sequences (bottom panel) during non-CAP (n-CAP), CAP, and REM.

\* $P < 0.05$  among sleep stages by ANOVA on ranks.

already been reported by our group<sup>25</sup> and is tentatively explained by the nonlinear properties of the baroreceptor reflex.<sup>26,27</sup> Specifically targeted additional studies are required for a finer definition of this issue. However, within the framework of the present investigation, it could be argued that the lack of changes in BRS in response to BP decrease could indicate that arterial baroreflexes act more to defend the lower HR of sleep rather than to oppose it.<sup>5,26,28</sup>

The analysis of sleep microstructure allowed us to make evident, for the first time to our knowledge, the occurrence of phases of sustained peripheral sympathetic activation, cleansed of arousal, similar to those of REM outlasting the transient sympathetic activation and BP increase induced by arousal stimuli ("K" complex<sup>5-7</sup>) and spread throughout the overnight asleep period. As in REM, sympathetic activation of CAP epochs was associated to buffering influences from arterial baroreflexes. In fact, during CAP,  $LF_{SBP}$  was significantly higher than during non-CAP, although to a lesser extent than during REM, and was associated with a significant increase in BRS up-sequences (Figure 4), with no significant difference in RRI, similarly to what emerged from the analysis of sleep macrostructure. A relevant difference between REM and CAP conditions was detected in the autonomic modulation of the sinoatrial node. In fact, whereas the HF component (nu) of HRV decreased and the LF component (nu) increased during REM in comparison to the global non-REM sleep, LF (nu) did not change significantly during CAP as compared with non-CAP conditions, and HF (nu) showed a slight increase. The finding of an increase in  $LF_{SBP}$  without a concomitant change in the LF component of HRV would implicate a differential control of cardiac and peripheral sympathetic outflow during CAP, in line with the emerging concept of selectivity of autonomic regulation.<sup>28-30</sup> Clearly, the brain neurophysiological patterns of CAP are different from REM.<sup>31</sup> CAP epochs occur during sleep stages (that is, non-REM) characterized by an already heightened level of background cardiac vagal activity that may dampen cardiac sympathetic activation, as indicated by the significantly greater and lower mean values of the HF nu and LF nu components of HRV, respectively, during non-REM sleep stages as a whole in comparison with the corresponding CAP epochs (Table 2).

Our finding of no significant changes in cardiac autonomic modulation between CAP and non-CAP conditions are at variance with the limited previous studies, which reported increases in LF and decreases in HF RRI oscillations during CAP.<sup>10,11</sup> The reasons for these discrepant findings are not readily apparent but may relate, in part, to the much younger age of subjects included in one study,<sup>11</sup> because aging significantly affects structural organization of sleep.<sup>31</sup> Unfortunately, in both these studies, autonomic vascular modulation and baroreflex control of HR have not been assessed, making a comparison with our results difficult.

Clearly, regulation of sinoatrial node during sleep cannot be simply equated to an increase in sympathetic predominance in REM and an increase in parasympathetic predominance in non-REM sleep. Generalization of autonomic output from a single autonomic parameter should be performed with caution.

A potential limitation of this study includes the indirect method used to assess changes in autonomic function. The issue of the validity of this approach was recently addressed by experiments in humans<sup>22</sup> in whom direct recordings of muscle sympathetic nerve activity were performed during various states of autonomic regulation, as produced by graded infusions of vasodilators and vasoconstrictors. The presence of similar, coherent, oscillations at low- and high-frequency in nerve activity, RRI, and SBP variabilities at various levels of induced pressure changes provides support to the use of  $LF_{RR}$  and  $HF_{RR}$  to infer the changing state of, respectively, sympathetic and vagal modulation of the sinoatrial node and of  $LF_{SBP}$  as an index of efferent sympathetic vascular modulation.<sup>22</sup>

### Perspectives

The findings of the present investigation could provide some clues into neural mechanisms for cardiac events during night. It has been shown that a great percentage of cardiac events, including myocardial infarction and sudden deaths, occur throughout the nocturnal period.<sup>1,2,32</sup> It has also been reported that myocardial ischemia occurring during sleep is not limited to REM, but may occur to a greater extent during SW sleep;<sup>33</sup> however, the underlying mechanisms have not been elucidated. A body of evidence indicates a link between increases in sympathetic activity and the increased risk for life-threatening arrhythmias, whereas increases in parasympathetic activity would reduce the risk for ventricular arrhythmias<sup>34,35</sup> and cardiovascular events.<sup>12</sup> Within the framework of studies with sleep staging, disappearance of nocturnal vagal predominance during non-REM sleep has been reported after myocardial infarction<sup>36</sup> and proposed as a significant factor in the nocturnal occurrence of fatal events. By converse, the increase in BRS by conferring protection against the surges of sympathetic activation might result in a condition less favorable for cardiac events. Because BRS increases during CAP times in combination with an increase in sympathetic activation, we speculate that disruption of this increased baroreflex gain during CAP, and in REM as well<sup>25</sup> (as may occur, for example, in ischemic and heart failure patients and in subjects with obstructive sleep apnea), might conceivably predispose to an increased likelihood of arrhythmic-ischemic events occurring throughout the sleep period and that this mechanism might contribute, in addition to others, to explain the nonuniform nighttime distribution of acute cardiac events.<sup>2</sup>

It is noteworthy that autonomic differences between CAP and non-CAP are present in stage 2 and in SWS, which generally occupy  $\approx 70\%$  of the total sleep time. Hence, microstructural phenomenon may impact extensively on neural cardiovascular regulation throughout sleep.

Limitations of the study include the small sample size and the lack of breathing pattern monitoring. Anyway, the differences observed across the different sleep stages were remarkably consistent and highly significant. As to the effect of respiration, we do not know to what extent changes in respiratory pattern that may occur during sleep could have affected HRV and BRS, inasmuch as we did not measure tidal volume. However, changes in breathing frequency at least should have not signif-

icantly influenced BRS and HRV parameters, because they did not differ among the different sleep stages.

In conclusion, our study dealing with sleep microstructure showed that sustained sympathetic activation, resembling that occurring during REM, does occur during non-REM sleep phases characterized by EEG-defined cycling alternating pattern and are associated to an increased BRS, eluding the reciprocal balance that conversely seems to characterize wakefulness. Simultaneous assessment of BRS and HRV according to sleep microstructure could prove helpful in identifying patients at increased risk for nocturnal events (eg, early postmyocardial infarction, impaired left ventricular function, obstructive sleep apnea syndrome)<sup>37</sup> and in guiding therapy effectively during the nighttime.<sup>1</sup> This would be possible with a complete, noninvasive, minimally disturbing approach.

### Acknowledgments

This study was supported in part by Ministero Dell'Università e Dell'Ricerca Scientifica e Tecnologica (COFIN 2003, ex quota 40%) and by the Agenzia Spaziale Italiana (grant ASI-I/R/062/01).

### References

- Verrier RL, Muller JE, Hobson JA. Sleep, dreams, and sudden death: the case for sleep as an autonomic stress test for the heart. *Cardiovasc Res.* 1996;31:181–211.
- Lavery CE, Murray MA, Mittleman A, Cohen MC, Muller JE, Verrier RL. Nonuniform nighttime distribution of acute cardiac events. A possible effects of sleep states. *Circulation.* 1997;96:3321–3327.
- Muller JE, Stone PH, Turi ZG, Rutheford GD, Czeisler CA, Parker C, Poole WK, Passamani E, Roberts R, Robertson T, Sobel BE, Willerson JT, Braunwald E. Circadian variation in the frequency of onset of acute myocardial infarction. *N Engl J Med.* 1985;313:1315–1322.
- Muller JE, Ludmer PL, Willich SN, Tofler GH, Aylmer G, Klangs I, Stone PH. Circadian variation in the frequency of sudden cardiac death. *Circulation.* 1987;75:131–138.
- Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects. *N Engl J Med.* 1993;328:303–307.
- Hornyak M, Cejnar M, Elam M, Matousek M, Wallin BG. Sympathetic muscle nerve activity during sleep in man. *Brain.* 1991;114:1281–1295.
- Okada H, Iwase S, Mano T, Sugiyama Y, Watanabe T. Changes in muscle sympathetic nerve activity during sleep in humans. *Neurology.* 1991;41:1961–1966.
- Terzano MG, Mancina D, Salati MR, Costani G, Decembrino A, Parrino L. The cyclic alternating pattern as a physiological component of normal NREM sleep. *Sleep.* 1985;8:137–145.
- Terzano MG, Parrino L, Spaggiari MC. The cyclic alternating pattern sequences in the dynamic organization of sleep. *Electroenceph Clin Neurophysiol.* 1988;69:437–447.
- Ferini-Strambi L, Bianchi A, Zucconi M, Oldani A, Castronovo V, Smirne S. The impact of cycling alternating pattern on heart rate variability during sleep in healthy young adults. *Clin Neurophysiol.* 2000;111:99–101.
- Ferri R, Parrino L, Smerieri A, Terzano MG, Elia M, Musumeci SA, Pettinato S. Cycling alternating pattern and spectral analysis of heart rate variability during normal sleep. *J Sleep Res.* 2000;9:13–18.
- La Rovere MT, Bigger JT Jr., Marcus FI, Mortara A, Schwartz PJ for the ATRAMI Investigators. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. *Lancet.* 1998;351:478–484.
- Rechtschaffen A, Kales A. *A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects.* Washington, DC: Public Health Service, U.S. Government Printing Office; 1968.
- Iellamo F, Legramante JM, Raimondi, Castrucci F, Massaro M, Peruzzi G. Evaluation of reproducibility of spontaneous baroreflex sensitivity at rest and during laboratory tests. *J Hypertens.* 1996;14:1099–1104.
- Iellamo F, Pizzinelli P, Massaro M, Raimondi G, Peruzzi G, Legramante JM. Muscle metaboreflex contribution to sinus node regulation during static exercise. Insights from spectral analysis of heart rate variability. *Circulation.* 1999;100:27–32.
- Bertinieri G, Di Rienzo M, Cavallazzi A, Ferrari AU, Pedotti A, Mancina G. Evaluation of baroreceptor reflex by blood pressure monitoring in unanesthetized cats. *Am J Physiol.* 1988;254:H377–H383.
- Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, Sandrone G, Malfatto G, Dell'Orto S, Piccaluga E, Turiel M, Baselli G, Cerutti S, Malliani A. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympathovagal interaction in man and conscious dog. *Circ Res.* 1986;59:178–193.
- Iellamo F, Legramante JM, Massaro M, Galante A, Pigozzi F, Nardozi C, Santilli V. Spontaneous baroreflex modulation of heart rate and heart rate variability during orthostatic stress in tetraplegics and healthy subjects. *J Hypertens.* 2001;19:2231–2240.
- Iellamo F, Legramante JM, Pigozzi F, Spataro A, Norbiato G, Lucini D, Pagani M. Conversion from vagal to sympathetic predominance with strenuous training in high performance world class athletes. *Circulation.* 2002;105:2719–2724.
- Task Force of the European Society of Cardiology and the North Am Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. *Circulation.* 1996;93:1043–1065.
- Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. *Circulation.* 1991;84:482–492.
- Pagani M, Montano N, Porta A, Malliani A, Abboud FM, Birkett C, Somers VK. Relationship between spectral components of cardiovascular variabilities and direct measures of muscle sympathetic nerve activity in humans. *Circulation.* 1997;95:1441–1448.
- Conway J, Boon N, Jones JV, Sleight P. Involvement of the baroreceptor reflexes in the changes in blood pressure with sleep and mental arousal. *Hypertension.* 1983;5:746–748.
- Van de Borne P, Nguyen H, Biston P, Linkowski P, Degaute JP. Effects of wake and sleep stages on the 24-h autonomic control of blood pressure and heart rate in recumbent men. *Am J Physiol.* 1994;266:H548–H554.
- Legramante JM, Marciari MG, Placidi F, Aquilani S, Romigi A, Tombini M, Massaro M, Galante A, Iellamo F. Sleep-related changes in baroreflex sensitivity and cardiovascular autonomic modulation. *J Hypertens.* 2003;21:1555–1561.
- Mancina G, Mark AL. Arterial baroreflexes in humans. *Handbook of Physiology. The Cardiovascular System. Peripheral Circulation and Organ Blood Flow.* Bethesda, MD: American Physiological Society; 1983:755–793.
- Pickering TG, Gribbin B, Sleight P. Comparison of the reflex heart rate response to rising and falling arterial pressure in man. *Cardiovasc Res.* 1972;6:277–283.
- Somers V, Grassi G. The functional heterogeneity of sleep. *J Hypertens.* 2003;21:1455–1457.
- Pagani M, Iellamo F, Lucini D, Cerchiello M, Castrucci F, Pizzinelli P, Porta A, Malliani A. Selective impairment of excitatory pressor responses after prolonged simulated microgravity in humans. *Auton Neurosci.* 2001;91:85–95.
- Legramante JM, Galante A, Massaro M, Attanasio A, Raimondi G, Pigozzi F, Iellamo F. Hemodynamic and autonomic correlates of postexercise hypotension in patients with mild hypertension. *Am J Physiol.* 2002;282:R1037–R1043.
- Parrino L, Boselli M, Spaggiari MC, Smerieri A, Terzano MG. Cyclic alternating pattern (CAP) in normal sleep: polysomnographic parameters in different age groups. *Electroenceph Clin Neurophysiol.* 1998;107:439–450.
- Willich SN, Levy D, Rocco MB, Tofler GH, Stone PH, Muller JE. Circadian variation in the incidence of sudden cardiac death in the Framingham Heart Study population. *Am J Cardiol.* 1987;60:801–806.
- Broughton R, Baron R. Sleep patterns in the intensive care unit and on the ward after acute myocardial infarction. *Electroenceph Clin Neurophysiol.* 1978;45:348–360.
- Malliani A, Schwartz PJ, Zanchetti A. Neural mechanisms in life-threatening arrhythmias. *Am Heart J.* 1980;100:705–715.
- Schwartz PJ, Vanoli E, Stramba-Badiale M, De Ferrari GM, Billman GE, Foreman RD. Autonomic mechanisms and sudden death: new insights from analysis of baroreceptor reflexes in conscious dogs with and without a myocardial infarction. *Circulation.* 1988;78:969–979.
- Vanoli E, Adamson PB, Lin B, Pinna GD, Lazzara R, Orr WC. Heart rate variability during specific sleep stages. A comparison of healthy subjects with patients after myocardial infarction. *Circulation.* 1995;91:1918–1922.
- Narkiewicz K, Montano N, Cogliati C, van de Born PJ, Dyken ME, Somers VK. Altered cardiovascular variability in obstructive sleep apnea. *Circulation.* 1998;98:1071–1077.