Sleep and Hypertension
A Challenge for the Autonomic Regulation of the Cardiovascular System

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Even though sleep is widely considered to be a restorative and refreshing process, it is characterized by complex activity of the cardiovascular autonomic mechanisms and by relevant changes of arterial pressure and heart rate. It has been widely reported that fluctuations and variability of cortical and visceral activities involve a differential autonomic regulation of the cardiovascular system in relationship to different sleep cycles. During non–rapid eye movement (REM) sleep, arterial pressure and heart rate tend to decrease, whereas periods of relative hypertension and tachycardia characterize REM periods. With regard to the cardiovascular autonomic modulation, non-REM sleep is characterized by a vagal predominance, whereas during REM sleep, a relative increase in sympathetic activity is demonstrated by an increased sympathetic outflow to muscle blood vessels.1–3

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Therefore, this continuous cycling of non-REM and REM phases, with the consequent cardiovascular autonomic changes, makes sleep a period of considerable physiological turbulence characterized by sudden and abrupt blood pressure and heart rate changes. This cardiovascular instability has stimulated the investigation of the neural mechanisms involved in maintaining the cardiovascular homeostasis during the different sleep phases. The first pivotal study conducted with the Oxford technique in normotensive and hypertensive subjects4 clearly showed that changes in baroreflex function investigated by quantifying the reflex RR interval lengthening in response to a pharmacologically induced increase in systolic blood pressure (obtained through intravenous injection of phenylephrine), occurred ongoing from wakefulness to sleep. These changes consisted of an increase in the reflex sensitivity and of a resetting, moving the operating point of the reflex toward lower blood pressure values.4 In the past few years, this issue has been further investigated because it is now possible to investigate the arterial baroreflex function by analyzing the correlated blood pressure and spontaneous heart rate fluctuations, thus avoiding external perturbations of the cardiovascular system.5 Two recent studies conducted in healthy subjects6,7 have shown that the arterial baroreflex function controlling the sinus node during sleep is more complex. Even confirming a relative increase of the baroreflex sensitivity (BRS) ongoing from wakefulness to sleep, the arterial baroreflex control of sinus node has been demonstrated to be more active in response to baroreflex activation, as occurs during hypertensive stimuli, thus highlighting its braking effect in response to sympathetic activation occurring during REM. Furthermore, a different behavior of the baroreflex control of sinus node has been demonstrated between early and late sleep cycles, with increased baroreflex sensitivity in response to hypertensive stimuli being evident during REM in the late phase of sleep, close to morning awakening but not in the early cycles of sleep in which a greater sympathetic activation6 was evident. Thus, these findings suggest that the arterial baroreflex is more effective in buffering the increased blood pressure and sympathetic activation associated with REM episodes occurring at the end of the sleep period, before morning awakening, than early in the night. The authors hypothesized that this decreased reflex antagonism of sympathetic activation may contribute to the genesis of cardiovascular adverse events occurring early in the night because of the fact that despite the anecdotal report of an increase of cardiovascular events in the last part of the night, Laverty et al8 observed a nonuniform distribution during the night, with the peak incidence of myocardial infarction and sudden cardiac death in the first part of the night.

In line with these findings, other studies report that sleep disturbances and disorders (ie, sleep-related breathing disorders) may represent potential contributors to the initiation and progression of cardiovascular disease.9,10 Furthermore, sleep deprivation may cause an increase in blood pressure.11 Consequently, there is much evidence to support a strong correlation between sleep and cardiovascular diseases. In particular, the pathogenesis of hypertension seems to be strikingly linked to sleep pathophysiology. It is well known that hypertensive subjects in whom the nocturnal blood pressure fall appears to be blunted (nondipper subjects) may develop a higher degree of target organ damage and/or more frequent cardiovascular events.12,13 Finally, pathophysiological mechanisms present in different sleep disturbances such as obstructive sleep apnea and central sleep apnea (including sympathetic activation, endothelial dysfunction, and oxidative stress) may influence the development and progression of cardiac and vascular pathology.14 In particular, the prevalence of hypertension is greater in patients affected by obstructive sleep apnea, and hypertensives are more likely to have obstructive sleep apnea than are nonhypertensives.15,16
A novel approach to the issue of the interaction between sleep and hypertension has been used by Kuo and colleagues in an original and interesting study in this issue of Circulation addressing the autonomic neural regulation of cardiovascular function during sleep in spontaneously hypertensive rats (SHR) rats in comparison with normotensive WKY controls. Using a telemetry transmitter system, the authors monitored arterial pressure signals in unrestricted rats and evaluated the changes of arterial pressure variability, thus extrapolating indirect indices of autonomic modulation of sinus node and vascular tone. Simultaneously, the electroencephalogram (EEG) and the electromyogram (EMG) were monitored to provide a detailed classification of states of consciousness, such as waking and sleeping. The authors designed this study on the basis of 2 main considerations: (1) Studies investigating the cardiovascular autonomic regulation in hypertensives have not reported uniform results because sympathetic function has been reported as higher, simlar, or even decreased as compared with normotensives; and (2) the multifactorial and complex mechanisms underlying the pathogenesis of hypertension have caused investigators to use a large number of animal models, such as the SHR rat, in the study of the cardiovascular autonomic regulation in particular.

Kuo and colleagues attempted to test the novel and interesting hypothesis that these conflicting results could be caused, at least in part, by the changes in the cardiovascular autonomic regulation during different states of consciousness, such as waking and sleeping. The brilliant and innovative experimental design and methodology (ie, polysomnographic recordings coupled with telemetric arterial pressure recordings) allowed the authors to investigate the effect of the different sleep stages on sympathetic vasomotor control and on baroreflex function as indirectly assessed through the analysis of arterial pressure and heart rate variability in freely moving unanesthetized SHR rats as compared with normotensive controls.

The more intriguing finding is that the cardiovascular autonomic pattern in SHR rats is strictly linked to the consciousness state. Whereas the indirect indices of sympathetic vasomotor control are similar between SHR rats and normotensive controls when awake, SHR rats show a substantially and significantly higher peripheral sympathetic outflow during sleep. Together with these observations, the authors report a BRS increase during sleep as compared with the awake state, which occurs both in WKY normotensive controls, as reported by previous studies in humans, and to a lesser extent in SHR rats. The key point, however, is the observation that whereas during the awake state BRS was similar between SHR and WKY rats, during sleep the baroreflex function was significantly depressed in hypertensive rats.

It is noteworthy that after the pivotal reports of the Oxford group, this is the first study in which the baroreflex control of sinus node has been evaluated in hypertensive subjects in a noninvasive and nonperturbational way. This is not a trivial point because as remarked by Kuo and colleagues, when BRS is evaluated by producing arterial pressure changes through the injection of drugs (ie, phenylephrine, nitrporus-

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