

To Dip or Not to Dip On the Physiology of Blood Pressure Decrease During Nocturnal Sleep in Healthy Humans

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Abstract—That sleep is accompanied by a blood pressure decrease is well known; however, the underlying physiology deserves further investigation. The present study examines in healthy subjects 2 main questions: is this dipping actively evoked? and what are the consequences of nondipping for daytime blood pressure? Nocturnal blood pressure was extrinsically elevated in 12 sleeping subjects to mean daytime values by continuously infused phenylephrine. This nondipping significantly lowered morning blood pressure during rest and 3 hours after resuming physical activity compared with a control condition (isotonic saline). Neither muscle sympathetic nerve activity nor sensitivity of α -adrenoceptors was reduced. However, the set point for initiation of regulatory responses through the baroreflex was clearly shifted toward lower blood pressure levels. Our results support the hypothesis of an actively regulated central mechanism for blood pressure resetting and set point consolidation of the baroreflex during nighttime sleep. This is suggested by the fact that extrinsically induced nondipping induces sustained decrease in blood pressure during the following morning through an actively lowered baroreflex set point. (*Hypertension*. 2007;49:1070-1076.)

Key Words: dipping ■ baroreflex ■ microneurography ■ MSNA ■ sympathovagal balance

Blood pressure fluctuates considerably throughout the circadian period with a clear decrease during sleep. This blood pressure dipping regularly exceeds 10% of mean daytime values in normotensive and primary hypertensive subjects.^{1,2} Dipping seems to be important for cardiovascular health, and its disturbance accelerates the development of cardiovascular diseases. In nondipping conditions like the obstructive sleep apnea syndrome, sympathoexcitation and arterial hypertension develop.^{3,4} Nocturnal blood pressure may also affect the morning surge of blood pressure,^{5,6} which has been alleged for the sleep association and early morning preponderance of vascular accidents in predisposed persons.^{7,8}

It is well known that the sleep-related blood pressure decline is the result of a downward shift of the baroreflex threshold. This threshold defines the blood pressure at which counterregulatory modulation of sympathetic nerve activity to the muscle vascular bed or the heart is initiated.⁹⁻¹² The consequence of this shift is a reduced sympathetic activity^{5,13-15} together with a blood pressure decline during sleep. However, it is unclear whether this shift in baroreflex function is actively induced or whether it is merely the passive consequence of sleep-inherent physical and cognitive inactivity.¹⁶⁻¹⁸ An active sleep-induced blood pressure lowering would be of considerable interest, because it might represent a unique endogenous mechanism that cannot be

observed during wakefulness. Its understanding might offer new insight into the physiology and pathophysiology of blood pressure regulation in humans.

In the present study we hypothesized that an active blood pressure-lowering mechanism could be unmasked when the nocturnal blood pressure was increased to daytime values. In case of an active nocturnal downregulation, extrinsically induced nondipping would be opposed by counterbalancing responses. On the other hand, if nocturnal dipping was a passive phenomenon, counterregulation would not occur. Rather, adaptation of the baroreflex to elevated blood pressure levels would result in a loss of baroreflex sensitivity with the consequence of increased daytime blood pressure. Thus, we expected that both active or passive mechanisms of nocturnal blood pressure dipping would differentially affect blood pressure regulation in the morning when blood pressure was extrinsically increased to mean daytime levels during nocturnal sleep. Therefore, we evaluated morning blood pressure, muscle sympathetic nerve activity, and baroreflex function in normotensive subjects after nocturnal infusion of the peripherally acting α -adrenoceptor agonist phenylephrine.

Methods

Subjects

Twelve healthy normotensive volunteers (6 men and 6 women) participated in the experiments. Subjects were nonsmoking, free of

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any medication, did not report any sleep disturbances, and had not worked on night shift ≥ 2 weeks before the experiments. In female subjects, experiments were performed in the first half of their ovulatory cycle. The day before the experiment, subjects abstained from caffeinated and alcoholic drinks but maintained their normal diet. The study was approved by the local ethics committee, and all of the participants gave written informed consent.

Subjects Preparation for Sleep Experiments

Subjects were adjusted to the experimental setting by spending 1 night under conditions of the experiment, including somnopolygraphy and continuous ECG monitoring. A venous catheter was inserted to allow drug administration during the experiment. During sleep, blood pressure was oscillometrically controlled. In addition, 24-hour ambulatory blood pressure was measured (20-minute intervals, SpaceLabs) the following day until 8:30 PM.

Design

Subjects participated in 2 experimental conditions, nighttime sleep with unaffected blood pressure dipping and with pharmacologically evoked nondipping. In a single-blinded design, the order of conditions was randomized and balanced across subjects; that is, half of the subjects started with the dipping night (control), whereas the other half started with the nondipping condition. Experimental sessions were separated by ≥ 1 week.

In the evening, resting blood pressure was repeatedly measured during relaxed wakefulness in a comfortable supine position. Lights were turned off at 11:30 PM to enable sleep. After onset of sleep, continuous infusion of either normal saline (placebo) or phenylephrine (1%) was started. Doses of phenylephrine infusion were adjusted according to intermittently recorded oscillometric blood pressure values during sleep to increase the nocturnal blood pressure to the levels determined in the wake supine subjects before sleep. Subjects woke up spontaneously before 6:30 AM or were gently awoken at that time. Subsequently, subjects were asked to void urine to reduce confounding effects of bladder distension on sympathetic nerve activity.¹⁹ Subjects remained in a horizontal position until the end of the experiment at 10:00 AM. During this period, microneurographic recording and baroreflex testing were performed. Blood was sampled in the evening 60 minutes before sleep and immediately after awakening in the morning. Blood samples were immediately centrifuged and the plasma or serum stored at -80°C until assay.

Muscle Sympathetic Nerve Activity Recordings

Participants were investigated in a comfortable supine position. Multiunit recordings of efferent muscle sympathetic nerve activity (MSNA) were obtained using Tungsten microelectrodes as described in detail elsewhere.^{19–21} Analogue curves of all of the parameters were digitized online with a sampling frequency of 200 Hz and stored on a computer disk for subsequent analysis (PowerLab, ADInstruments).

Baroreflex Testing

Data sampling started with a 15-minute period for baseline recordings of MSNA, heart rate, heart rate variability (HRV), and oscillometric blood pressure. Subsequently, baroreceptor function was tested by the vasoactive drug method.¹⁰ In brief, incremental doses of sodium nitroprusside ($0.15 \text{ mg kg}^{-1} \text{ h}^{-1}$ to $0.35 \text{ mg kg}^{-1} \text{ h}^{-1}$ to $0.55 \text{ mg kg}^{-1} \text{ h}^{-1}$) or phenylephrine ($0.09 \text{ mg kg}^{-1} \text{ h}^{-1}$ to $0.21 \text{ mg kg}^{-1} \text{ h}^{-1}$ to $0.30 \text{ mg kg}^{-1} \text{ h}^{-1}$) were intravenously infused. Each dose step was maintained for 5 minutes. The nitroprusside and phenylephrine infusion was separated by a 15-minute washout interval.

Biochemistry

Plasma/serum renin, angiotensin II, aldosterone, endothelin-1, and vasopressin were determined using commercial assays. Serum osmolality and electrolytes were measured according to standard techniques.

Sleep Recordings

Somnopolygraphical recordings were scored offline according to the criteria of Rechtschaffen and Kales.²² For each night, total sleep time (in minutes) and the percentage of time spent in different sleep stages (wakefulness, sleep stages 1 and 2, slow wave sleep [SWS], and rapid eye movement sleep [REM]) were determined with reference to total sleep time. Total sleep time lasted from sleep onset, defined as the onset of the first sleep stage 1 epoch followed by sleep stage 2 sleep, until final awakening. In addition, the first and second halves of the night were subanalyzed.

Ambulatory Blood Pressure Monitoring

Mean nighttime blood pressure values were compared with the mean daytime levels of the placebo condition to document that all of the participants physiologically dipped during the placebo night and that dipping was successfully prevented during the nocturnal phenylephrine infusion. Subsequently, daytime blood pressure levels after the dipping and nondipping sleep were compared.

Baroreceptor Set Point and Sensitivity

MSNA, heart rate, and oscillometric blood pressure were evaluated in the morning during the following: (1) the initial 15-minute baseline period, (2) the last minute of each dosing step of the nitroprusside, and (3) the phenylephrine phase of the baroreceptor modulation, respectively. All of the recordings were analyzed by the same observer, who was unaware of the nocturnal dipping or nondipping condition. Sympathetic bursts were visually identified by inspecting the mean voltage neurogram, and MSNA was quantified with the aid of analytical software (Chart 5.02, ADInstruments) that also analyzed heart rate from the ECG. A recording was considered suitable for analysis when the signal/noise ratio was >3 . Nerve activity was expressed as the number of bursts per minute. Individual baroreflex sensitivities were calculated by dividing changes in MSNA or heart rate by changes in mean arterial pressure and comparing data of both ends of the vasoactive drug test.

Frequency domain measurements of HRV were calculated from 5-minute recordings of the baseline period and during the final 5-minute dosing step of nitroprusside and phenylephrine of baroreceptor modulation. The limits of low frequency and high frequency were defined at 0.04 to 0.15 Hz and >0.15 Hz according to task force standards.²³

Statistics

Individual values of MSNA, HRV, cardiovascular measures, and biochemical parameters were averaged for each condition and expressed as mean \pm SEM. Statistical analysis was based on ANOVA with the repeated measures factor "time" and the group factor "treatment" (phenylephrine versus placebo). When the overall analysis indicated significance, posthoc testing was performed, and a Greenhouse–Geisser corrected $P < 0.05$ was considered significant (SPSS for Windows). Data recorded during baroreflex testing were fitted to 4-parameter logistic functions for both experimental conditions to obtain sigmoid regression curves.

Results

Characteristics of Nighttime Sleep

Total sleep time was not changed by the infusion of phenylephrine. However, the percentage of intermittent wakefulness was slightly increased, and SWS was reduced as compared with the control night (wake: $5.1 \pm 1.5\%$ versus $1.8 \pm 0.6\%$; SWS: $17.2 \pm 2.0\%$ versus $21.9 \pm 2.3\%$; $P < 0.05$). This difference was confined to the first half of sleep (SWS: $22.8 \pm 3.8\%$ versus $33.0 \pm 4.4\%$; $P < 0.05$), whereas there were no significant differences during the second half (SWS: $10.8 \pm 2.3\%$ versus $11.6 \pm 1.7\%$; P value not significant). The percentage of sleep stage 1, sleep stage 2, and rapid eye movement sleep was not significantly affected by phenylephrine.

TABLE 1. Heart Rate and Oscillometric Blood Pressure (mean±SEM) in 12 Normotensive Subjects Before and During Nighttime Sleep, After Awakening in the Morning While Resting in a Supine Position, and After Arising and Resuming Normal Day Activity

Parameters/Recording Period	Control	Nondipping
Heart rate, bpm		
Wake before sleep	64.0±1.4	66.6±2.6
Sleep period	62.3±2.6*‡	54.8±2.9*
Wake after sleep (supine)	66.1±2.4	71.0±3.7
Ambulatory HR hour 0 to 3	92.1±3.5	95.4±4.5
Ambulatory HR hour 3 to 6	84.5±3.6	88.0±5.2
Systolic BP (mm Hg)		
Wake before sleep	121.5±2.0	121.2±1.5
Sleep period	110.3±2.5*‡	123.6±2.3
Wake after sleep (supine)	115.8±3.9‡	110.2±3.3
Ambulatory BP hour 0 to 3	125.0±2.8†	117.2±3.3
Ambulatory BP hour 3 to 6	119.9±2.8	117.2±2.7
Mean art. BP (mm Hg)		
Wake before sleep	87.8±1.5	88.8±1.4
Sleep period	77.9±1.9*‡	89.7±2.2
Wake after sleep (supine)	85.9±2.8‡	81.2±2.4
Ambulatory BP hour 0 to 3	92.9±2.5†	87.9±2.0
Ambulatory BP hour 3 to 6	89.5±2.5	87.9±2.0
Diastolic BP (mm Hg)		
Wake before sleep	71.8±1.4	72.2±1.4
Sleep period	60.8±1.7*‡	73.6±2.2
Wake after sleep (supine)	70.9±2.4†	66.7±2.1
Ambulatory BP hour 0 to 3	76.4±2.1†	72.2±1.8
Ambulatory BP hour 3 to 6	73.3±2.5	72.1±2.1

HR indicates heart rate.

* $P<0.001$ for pairwise comparison of nighttime and ambulatory daytime values; † $P<0.05$, ‡ $P<0.01$ for comparison between the nondipping and dipping (control) condition.

Blood Pressure and Heart Rate Profiles

Evening blood pressure and heart rate before the phenylephrine or placebo infusion did not differ (see Table 1). Systolic, diastolic, and mean arterial blood pressure significantly dipped by $>10\%$ during normal nighttime sleep (control condition) as compared with the mean values of the following day ($P<0.001$ for the factor “time”; Table 1 and Figure 1). Phenylephrine infusion, on the other hand, successfully elevated nocturnal blood pressure to daytime levels (factor “time”: P value not significant). Heart rate was significantly lower at night in both groups ($P<0.001$ for the factor “time”). However, during phenylephrine infusion, nocturnal heart rate was lower as compared with placebo ($P<0.01$ for the group factor “treatment”; Figure 1 and Table 1).

After awakening and before any orthostatic challenge, blood pressure was significantly lower after nondipping compared with the dipping condition (systolic $P<0.05$; diastolic $P<0.01$; mean $P<0.05$), whereas heart rate did not differ significantly. This significant lowering of blood pressure persisted in the nondipping condition for an additional 3 hours after subjects left the laboratory (mean $P<0.05$ for the

group factor “treatment”). Thereafter, differences in blood pressure disappeared. After nondipping, heart rate was significantly higher immediately after arising (103.7 ± 5.8 versus 88.2 ± 2.7 ; $P<0.05$), but not in the supine resting subjects.

Baroreflex Testing

Despite the clear blood pressure decrease after extrinsic nocturnal nondipping, resting MSNA, heart rate, and frequency domain measures of HRV did not differ in the resting awake subjects during the baseline period (Table 2). Total power of HRV at supine rest was 4565.5 ± 842.7 ms² (mean±SEM) after nondipping and 3722.0 ± 644.6 ms² in the control condition (P value not significant). Normalized units of low frequency domain were 59.9 ± 4.4 versus 53.9 ± 4.8 (P value not significant), high frequency domain was 36.5 ± 4.1 versus 41.0 ± 4.4 (P value not significant), and the low frequency/high frequency ratio was 2.20 ± 0.50 versus 1.72 ± 0.33 (P value not significant), respectively.

Nitroprusside Infusion

The 3 incremental doses of nitroprusside caused a progressive decrease in blood pressure together with an increase in heart rate and MSNA. This was not changed after the nondipping night leading to similar net changes of blood pressure in both treatment conditions. Thus, the blood pressure difference observed at baseline persisted throughout all of the dose steps of nitroprusside infusion. MSNA, heart rate, and HRV (data not shown), however, did not differ between both experiments.

Phenylephrine Infusion

Incremental doses of phenylephrine resulted in a progressive elevation of blood pressure without any significant differences regarding absolute or net values between the treatment conditions. Concomitantly, MSNA and heart rate were reduced. Referring to baseline values, the net decrease of the heart rate was significantly stronger after nondipping sleep as compared with the control condition ($P<0.05$), whereas the reduction of MSNA did not differ between both experiments. Frequency domain data of HRV (not shown) did not display any difference between both conditions.

To further characterize the vascular baroreceptor–reflex set point and sensitivity, MSNA was correlated to the corresponding blood pressure values at baseline (unaffected rest) and during baroreceptor stimulation or deactivation, respectively, as demonstrated in Figure 2. Evidently, the set point of the vascular baroreflex and the stimulus–response curve were displaced to the left after nocturnal nondipping as compared with the control condition, thus, indicating a resetting of the baroreflex to a lower blood pressure level. Figure 2 also indicates that the blood pressure response to phenylephrine was not dampened.

Serological Parameters/Vasoactive Hormones

Although evening plasma renin and angiotensin II concentrations before both sleeping conditions were similar, morning values were significantly lower after nondipping sleep as compared with placebo (renin: 3.6 ± 0.3 versus 7.3 ± 0.9 ng/L, $P<0.01$; angiotensin II: 1.8 ± 0.2 versus 4.2 ± 0.9 pg/mL,

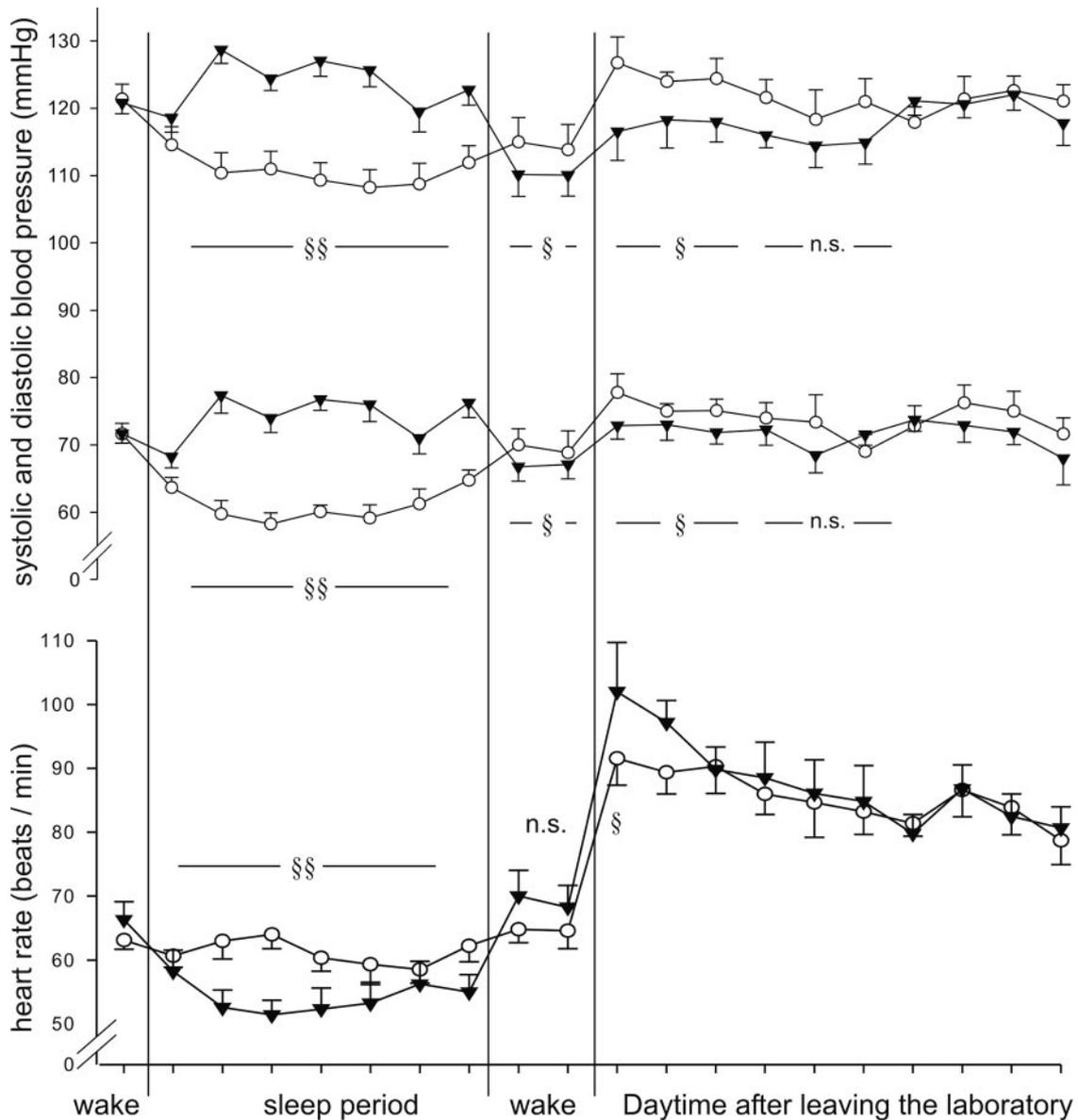


Figure 1. Systolic and diastolic blood pressure and heart rate of 12 normotensive volunteers receiving either phenylephrine to prevent nocturnal dipping (▼) or placebo (○). Blood pressure was oscillometrically measured every 20 minutes and averaged per hour starting in the evening before sleep. Recordings were continued after awakening while resting in a supine position (indicated by the vertical lines) and after resuming normal daytime activity. Values are expressed as mean \pm SEM. §§ P <0.01, § P <0.05, n.s. indicates nonsignificant for comparison between the nondipping and dipping condition.

P <0.05). Aldosterone levels, endothelin-1, vasopressin, serum osmolality, and electrolyte concentration did not differ significantly.

Discussion

Nocturnal sleep is characterized by a prolonged blood pressure decrease. Sleep onset induces characteristic changes in autonomic and endocrine functions with a reduction in sympathetic outflow to the heart and muscle vascular bed combined with a reduced activity of the renin-angiotensin system.^{5,9,13-15,24} Simultaneously, parasympathetic activity to the heart is increased.^{2,9,15} Several studies suggested that nocturnal blood pressure dipping is caused by a shift of the baroreflex set point toward lower blood pressure levels.^{9,14,17} However, the question remains unresolved regarding whether

this is an active process or the mere consequence of physical inactivity and sleep-related deprivation from external stimuli.

To solve this question, we overrode the physiological decrease in sympathetic activity by a continuous infusion of phenylephrine, an α -adrenoceptor agonist that does not pass the blood-brain barrier.²⁵ This disturbance of sleep-related dipping induced a strong counter-regulation with a shift of the baroreflex threshold toward lower blood pressure levels, which conveyed to the wake period sustaining several hours even in active, nonrestricted subjects.

Loss of peripheral α -adrenergic responsiveness to endogenous catecholamines does not account for the present findings. Once the phenylephrine dose was titrated to a predetermined average daytime level, blood pressure remained constantly increased throughout the night without further

TABLE 2. Baseline, Final-Dose Absolute Values and Maximal Relative Changes of Heart Rate, Oscillometric Blood Pressure, and MSNA (mean±SEM) in 12 Supine Normotensive Volunteers During Baroreflex Testing With Incremental Doses of Nitroprusside and Phenylephrine in the Morning

Parameters/Recording Period	Control	Nondipping
Mean arterial BP, mm Hg		
Baseline	85.9±2.8	81.2±2.4*
Nitroprusside		
Absolute	76.2±2.8	71.0±2.7*
Δ from baseline	-9.7±1.8	-10.2±2.0
Phenylephrine		
Absolute	94.1±4.0	93.5±2.2
Δ from baseline	+8.2±2.3	+12.3±1.9
MSNA, bursts per min		
Baseline	21.8±1.6	18.7±1.8
Nitroprusside		
Absolute	42.3±3.4	42.3±4.5
Δ from baseline	+22.4±1.8	+25.2±3.1
Phenylephrine		
Absolute	4.0±1.8	4.2±2.5
Δ from baseline	-17.4±1.9	-14.5±2.0
Heart rate, bpm		
Baseline	66.1±2.4	71.0±3.7
Nitroprusside		
Absolute	84.3±3.0	87.7±3.7
Δ from baseline	+18.3±1.7	+16.7±2.2
Phenylephrine		
Absolute	56.0±2.4	55.4±3.0
Δ from baseline	-10.1±3.0	-15.2±2.3*

* $P < 0.05$ for comparison between the nondipping and dipping (control) condition.

adjustment of the phenylephrine dose. This indicates that there was no significant desensitization of α -adrenoceptors. This was confirmed again by the observation that phenylephrine induced a similar pressor response during baroreflex testing in the morning independent from the fact of whether it was infused during the previous night or not.

Sleep disturbances are also unlikely to explain the present results. Phenylephrine infusion induced a subtle increase in wakefulness in parallel to a reduction of SWS. These effects, however, were restricted to the first half of total sleep time, and it is unlikely that this small effect sustained throughout the second half of the night. Previous studies consistently demonstrated that total^{17,26} or partial^{6,27} sleep deprivation resulted in increased blood pressure the next day, whereas the subjects in our study with less SWS had lower blood pressure levels.

Our study points to the fact that homeostatic mechanisms aim to actively reduce blood pressure during nighttime sleep. Under normal conditions, the primary dipping mechanism obviously is sympathoinhibition. However, when this mechanism is overridden (eg, phenylephrine infusion), counter-regulatory systems are recruited that possess sustained blood pressure-lowering effects even after termination of sleep.

The physiological basis of this phenomenon involves the baroreflex regulation of sympathetic nerve activity. On the first view, the absolute number of sympathetic bursts to the muscle vascular bed was not significantly affected by the nocturnal nondipping. However, MSNA is tightly regulated through the baroreflex arch and must be interpreted in relation to the prevailing blood pressure. Similarly, the cardiac baroreflex should correlate blood pressure to heart rate.^{10,28,29} The fact that, in the present study, daytime blood pressure was lowered by extrinsic nondipping, whereas MSNA was unaffected, clearly demonstrates that the vascular baroreflex is shifted to lower blood pressure values. This was confirmed by a baroreflex test using the infusion of vasoactive substances to increase or decrease blood pressure. This test not only allows us to determine the baroreflex set point but also baroreflex sensitivity illustrated by the slope of the correlation curve between blood pressure and MSNA or heart rate over the given blood pressure range induced by the vasoactive drugs.^{10,28,30} As outlined above, the slope of the vascular baroreflex was not changed after nocturnal infusion of phenylephrine, which indicates normal responsiveness of adrenoceptors. However, the baroreflex curve was shifted toward lower blood pressure levels throughout the whole blood pressure range. This shift most likely explains the sustained blood pressure decrease after extrinsic nondipping.

The sustained blood pressure decrease for 3 hours even after resuming physical activity argues against the assumption that baroreflex mechanisms only buffer rapid blood pressure changes. Early studies indicated that the baroreflex arch has little to no influence on long-term control, which is in part because of its ability to reset.^{11,30} Resetting was defined as an adaptive shift of the operating range of the baroreceptors in the direction of the prevailing blood pressure. Our study struggled with this view, because such resetting would have resulted in a shift of the baroreflex curve to the right (ie, to higher blood pressure levels) after the prolonged nocturnal blood pressure elevation. The shift to the left (ie, lower blood pressure levels) found in our study suggests that the nocturnal baroreflex set point in healthy normotensive subjects is actively regulated.

Our findings argue in favor of the recently proposed concept of a central nervously determined set point, which governs the peripheral baroreflex arch.^{31,32} It seems that the nocturnal sleep period uniquely allows the determination of this centrally driven set point, because wakefulness inevitably blurs or continuously modifies arterial baroreflex function. Recent animal studies highlighted the possibility of such a central nervous set point,³¹ and our study suggests that such superordinated central nervous control of baroreflex function exists in humans as well. Interestingly enough, Pattoneri et al³³ reported of sympathovagal imbalances in the control of vasomotor tone leading to a nondipping pattern in patients with persistent vegetative stage after traumatic brain injury. These findings further indicate the central nervous hierarchy of blood pressure control in humans. This system involves the integration of multiple inputs, including endocrine influences through the circumventricular organs, effects of body fluids osmolality and electrolyte concentration, and cardiovascular pressure reflexes.^{2,20,24,29,31,32,34,35} Interestingly, morning

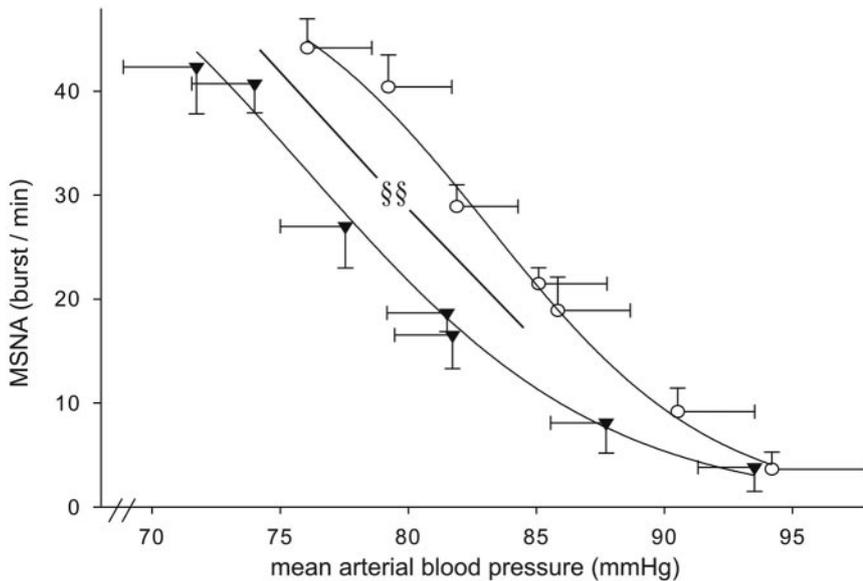


Figure 2. Visual correlation between MSNA and blood pressure at baseline and during blood pressure modulation via the infusion of phenylephrine or nitroprusside to characterize the vascular baroreceptor set point and sensitivity. Nondipping: ▼; dipping: ○. §§ $P < 0.01$ for pairwise comparison of the respective blood pressure values between both experimental conditions (ANOVA, group factor treatment).

sympathovagal balance to the heart, represented by the frequency domain of HRV, was not modified by the long-term infusion of phenylephrine, and changes in spectral power in response to baroreflex testing appeared maintained in the expected direction. The heart rate response to blood pressure changes always integrates effects of both sympathetic and parasympathetic activity, the latter being only indirectly involved in blood pressure control, particularly during nighttime sleep. This differential regulation of the vascular and the cardiac branch of the baroreflex is consistent with findings that nocturnal blood pressure dipping is not necessarily linked to the nighttime decrease in heart rate.³⁴

Maintaining nocturnal blood pressure elevated to unphysiological values with intravenous vasoconstrictors predominantly addresses 1 of the possible pathways involved in the circadian blood pressure profile.^{29,35} Our experimental model focused on the regulation of efferent sympathetic activity to the muscle vascular bed, being the most important vasoconstrictive stimulus, and modulated by sleep. This allows us to draw very specific conclusions concerning this branch of the baroreflex arch, whereas other aspects, particularly concerning cardiac baroreflex function, cannot be answered with similar specificity.²⁹ Obviously, microneurographic approaches to assess baroreflex gain represent a simplified input–output relationship of blood pressure and MSNA, which may potentially be modulated by effects of the drugs administered, independent from their blood pressure effects.³⁶ This simplification, however, was deliberately chosen as a scientific model dissecting important contributors involved in sleep-related blood pressure regulation. The fact that the shift of the vascular baroreflex set point was observed in resting conditions and that it was confirmed over a wide range of blood pressure values during the infusion of 2 differently acting drugs, that is, phenylephrine and nitroprusside, respectively, makes it unlikely that our findings are unspecific or simply substance related. It is much more likely that our experimental model was able to unmask a new aspect of nocturnal blood pressure physiology implying long-lasting

effects during daytime. This principle, however, has to be confirmed in additional studies involving higher numbers of subjects.

Although morning heart rate, HRV, serum osmolality, and electrolyte concentration remained unchanged, renin and angiotensin II plasma levels were significantly reduced after the phenylephrine night. The renin–angiotensin system was recognized previously for its particular importance in blood pressure dipping and long-term baroreflex resetting.^{37–39} In previous studies, we were able to demonstrate that selective AT-receptor blockade led to downward shift of the baroreceptor set point.³⁸ Thus, the low morning angiotensin II levels might serve as one explanation for the shift of the baroreflex curve in the present study.^{32,40} This hypothesis, however, cannot be established with the present study, and it is well possible that the decrease in renin and angiotensin levels just reflects the passive consequence of nondipping but has no regulatory influence on baroreflex function.

Perspectives

In conclusion, our data suggest that blood pressure dipping during nighttime sleep is a matter of active downregulation and underline the importance of a physiological nocturnal dipping for blood pressure regulation during daytime. Any offense to this mechanism, like extrinsic nondipping, is strongly counterbalanced by the organism, even leading to decreased blood pressure levels the following day without fundamental alterations in autonomic balance and sympathetic responsiveness. The study points to the importance of superordinated central nervous mechanisms, which actively lower blood pressure during nocturnal sleep via baroreflex mechanisms. This offers a new perspective on the role of nocturnal sleep for blood pressure regulation under physiological and pathophysiological conditions.

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Disclosures

None.

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