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Arousals Are Frequent and Associated With Exacerbated Blood Pressure Response in Patients With Primary Hypertension

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BACKGROUND
Spontaneous arousals are relatively common during sleep, and induce hemodynamic responses. We sought to investigate the frequency and magnitude of blood pressure (BP) increases triggered by spontaneous arousals in patients with primary hypertension.

METHODS
We conducted a study in which we divided 18 nonobese, sedentary adults without sleep-disordered breathing into two groups, consisting of: (i) hypertensive (HT, $n = 8$) patients; and (ii) normotensive (NT, $n = 10$) controls. The groups were matched for age and body mass index. All subjects underwent full polysomnography with simultaneous monitoring of heart rate (HR) and beat-by-beat BP. Each subject's BP and HR were analyzed immediately before BP peaks triggered by spontaneous arousals during stage 2 of nonrapid eye movement sleep.

RESULTS
The total sleep time, sleep efficiency, and sleep structure in the two study groups were similar. In contrast, the number of arousals was significantly higher in the HT than in the NT group, at 25 ± 5 vs. 12 ± 3 events/h, respectively ($P < 0.05$). The HR of the HT and NT groups was similar before arousal (65 ± 3 bpm vs. 67 ± 3 bpm, respectively, $P < 0.01$) and increased significantly and similarly in the two groups upon arousal (to 79 ± 6 bpm vs. 74 ± 4 bpm, respectively, $P < 0.01$). Systolic and diastolic BPs were significantly higher throughout sleep in the HT than in the NT group. During spontaneous arousals, BP increased in both groups ($P < 0.05$). However, the magnitude of the increase in systolic BP was significantly greater in the HT than in the NT group (22 ± 3 mm Hg vs. 15 ± 3 mm Hg, $P < 0.05$).

CONCLUSIONS
Patients with hypertension who do not have sleep-disordered breathing have an increased cardiovascular burden during sleep, which may be due to the greater number of arousals and exacerbated systolic BP response that they experience during sleep. These novel findings may have cardiovascular implications in patients with hypertension.

Keywords: spontaneous arousal; sleep; hypertension; blood pressure.

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Humans spend a significant proportion of their lives in sleep. Sleep may be seen as a period of quiescence of the cardiovascular system with a progressive decrease in heart rate (HR) and blood pressure (BP) during nonrapid eye movement (NREM) sleep. Rapid eye movement sleep is associated with oscillations in BP and HR. However, NREM sleep constitutes more than 75% of total sleep time in healthy individuals, and BP is expected to decrease > 10% during sleep.[1,2] The physiological decrease in BP as evaluated by 24-hour ambulatory BP monitoring occurs not only in normotensive (NT) individuals, but also in hypertensive (HT) patients.[3] Over the past three decades, an increasing awareness has occurred of the relationship between hypertension and obstructive sleep apnea (OSA), a condition characterized by repetitive obstruction of the upper airways, causing intermittent hypoxia and arousals from sleep.[4] A significant proportion of HT patients have OSA[5] that may lead to nondipping of BP during sleep.[6] However, little attention has been given to the study of sleep in HT patients without OSA.

There is growing evidence that HT patients frequently have reduced sleep time and poor sleep quality that in theory may participate in a vicious cycle and further contribute to poor BP control.[3,7-8] Using a beat-by-beat technique, we have recently shown similar reductions in BP in NREM sleep in NT and HT individuals in whom sleep-disordered breathing was carefully excluded.[9] However, in study showing such reductions, neither the frequency of arousals not the BP response to arousals were investigated. In order to accomplish this goal, we reanalyzed, in the present study, the data from the previous study.[9] In addition, because of insufficient BP data during spontaneous arousals in 7 subjects in stage 2 (N2) of NREM sleep, we included 6 new participants

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in the present study. The hypothesis was that among individuals without OSA or other sleep disturbances, patients with primary hypertension not treated with medication have greater sleep fragmentation and a greater increase in BP during spontaneous arousal in N2 of NREM sleep than do NT individuals.

METHODS

Subjects

We studied both male and female subjects. All of the female subjects were taking oral contraceptives (low doses of ethinyl estrogen and progestin). Study subjects who had a history of circadian desynchrony (e.g. shift workers) or periodic leg movements were excluded. Study subjects who were older than 50 years or had a body mass index (BMI) > 27 kg/m^2, diabetes mellitus, cerebrovascular disease, arrhythmias, heart failure, valvular heart disease, renal failure, renovascular hypertension, or a history of smoking or alcohol abuse (2 or more drinks per day) were excluded from the study. Because the study focused on subjects without sleep-disordered breathing, all of the subjects included in the study were selected according to a history of a low risk of OSA and an absence of daytime somnolence, as evaluated with the Berlin Questionnaire[10] and Epworth sleepiness scale,[11] respectively. The Berlin Questionnaire classifies a subject as having a low or high risk of OSA on the basis of 3 categories, which include snoring characteristics, tiredness, and obesity or hypertension. A low risk of OSA with this questionnaire is based on none or only one of its categories being positive. The Epworth sleepiness scale asks subjects to rate the probability of their falling asleep in 8 different daily situations, on a scale of increasing probability ranging from 0 to 3 for each situation. A total score below 10 is consistent with an absence of excessive daytime sleepiness and therefore with a low risk for the presence of OSA.

The NT controls for the study were recruited from the Heart Institute staff or their relatives, and were selected on the basis of having similar values of BMI. Hypertension was carefully excluded in the NT control group. To exclude masked hypertension or "white-coat" hypertension, all NT subjects had at least three office BP measurements made by one of the study investigators (L.F.D.), in addition to three out-of-office BP measurements. The HT individuals were outpatients recruited from the Hypertension Unit of the Heart Institute of the University of São Paulo Medical School who met the exclusion criteria for the study. Secondary causes of hypertension[12] were excluded through medical history, physical examination, and screening laboratory tests of the entire HT group (estimated glomerular filtration rate, urine-sediment examination, captopril renal scintigraphy, and measurement of plasma renin activity, aldosterone, thyroid-stimulating hormone, catecholamines, and 24-hour urinary metanephrines). All HT patients had previously been diagnosed as having stage 1 or 2 hypertension according to the current guidelines for this.[12] Patients with resistant, accelerated (defined as a recent, significant increase in BP over baseline BP in association with target-organ damage based on funduscopic examination, such as flame-shaped hemorrhages or soft exudates, but without papilledema), or malignant hypertension were excluded. Antihypertensive medications were withdrawn 2 weeks before the study, as described in the report of our previous study[9] and by others.[13,14] Antihypertensive medications included diuretics (62.5%), angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers (62.5%), and calcium-channel blockers (12.5%).

Experimental protocol

The study subjects were asked to continue their usual daily activities before the experiment, including regular sodium intake. They were asked to avoid caffeine, alcohol, and naps on the day of the study. All participants were admitted to the sleep laboratory at 8PM. After a physical examination, monitoring equipment was attached, and study subjects went to bed around 10PM.

Measurements

A standard overnight polysomnographic study (EMBLA, Flaga hf. Medical Devices, Reykjavik, Iceland) was performed as previously described.[15,16] Respiratory signals were recorded by a piezoelectric thoracic belt placed around the patient's upper abdomen. No sleep-inducing medications were administered before the polysomnographic study.

Cardiovascular monitoring

In addition to standard polysomnography, all subjects underwent a continuous and simultaneous electrocardiographic recording of their beat-by-beat HR, BP, and respiratory signals. Respiratory signals were recorded with a piezoelectric thoracic belt placed around the patient's upper abdomen. These signals were recorded continuously with an analog-to-digital multichannel signal conditioner and amplifier/filter (AT/MCA-CODAS, DATAC Instruments, Akron, OH). Blood pressure was measured with the Portapres system (TNO Biomedical Instrumentation, Amsterdam, The Netherlands), allowing continuous, indirect, noninvasive measurements of beat-by-beat BP. This method has been shown to accurately estimate intra-arterial BP through its use of a height-correction unit to compensate for measurement of BP in the finger.[17] For the subject's comfort, the Portapres system alternates its measurements among different fingers every 30 minutes. We considered for analysis only stable periods of measured BP, excluding periods of body movement through polysomnography. All recordings (polysomnographic and cardiovascular) were synchronized through the use of two computers because of the limitation of the sample size per channel of the polygraph. The analogical signals were sampled at 1,000 Hz per channel and stored on a hard disk for subsequent analyses.

Data analysis

Sleep stages were scored according to the criteria of Rechtschaffen and Kales[18] and Iber *et al.*[19] Apnea was defined as a decrease of > 90% for at least 10 seconds in the peak thermal sensor excursion. Hypopnea was defined as a significant reduction (> 50%) in respiratory signals for at least 10 seconds in association with an arousal or oxygen desaturation of ≥ 3%. The apnea–hypopnea index (AHI) was calculated as the total number of respiratory events (apneas plus hypopnea) per hour of sleep. Study subjects who had an AHI > 5 events per hour of sleep were excluded from the study. Arousal from sleep was defined as an abrupt increase in the frequency of the electroencephalogram, including an increase in the frequency of alpha or theta waves or both and/or frequencies exceeding 16 Hz, lasting 3–15 seconds, and preceded by 10 seconds of stable sleep.[19]

The polysomnographic records were reviewed particularly in the N2 of NREM sleep. Four spontaneous arousals, with a minimum duration of from 3–15 seconds and comprising two arousals in the first and two in the last sleep cycle during NREM, were selected.

For each spontaneous arousal, beat-by-beat BP and HR responses were analyzed from 15 seconds before until 15 seconds after spontaneous arousal. The BP signal was processed to detect beat-by-beat values of systolic BP and diastolic BP through the use of Windaq software (DATAC Instruments Inc., Akron, OH). Heart rate was calculated as beats per minute.

The average systolic and diastolic BP, HR during spontaneous arousals, and the average of maximal values for systolic and diastolic BP and HR responses in four spontaneous arousals occurring in the N2 of NREM sleep were determined for all subjects. The magnitude of responses for hemodynamic variables was determined for each subject by subtracting the mean beginning value from the mean maximal values during spontaneous arousal. The time taken to initiate a systolic BP response and the time to reach the peak systolic BP response during spontaneous arousals were determined for each subject, and group means were calculated for the HT and NT groups. Additionally, the durations of spontaneous arousals were determined for each subject and group means were calculated. Arousals were identified through visual inspection by the same investigator, blinded to the HT and NT groups.

Statistical analysis

All calculations were performed with the STATISTICA statistical program (StatSoft Inc., Tulsa, OK). Data are presented as means ± SEM. The chi-squared test was used for categorical variables. To compare the hemodynamic patterns in the HT and NT study groups across the sleep-arousal phases (beginning values and maximal response), analysis of variance (ANOVA) with repeated measures was used to test the interaction of phase effect and group effect. When significance was found, Scheffe's post hoc comparison was used. An unpaired *t*-test was performed to compare changes among groups. A Pearson correlation was done between the maximal systolic BP value during arousal and the duration of arousal for each study group. A value of $P < 0.05$ was considered statistically significant.

RESULTS

The characteristics of the study participants are shown in Table 1. The two study groups had similar, ages, BMIs, neck circumferences, and percentages of white members. The sleep parameters of the participants are shown in Table 2. The Epworth Sleepiness Score, total sleep time, sleep efficiency, sleep stages, AHI, and awakenings were similar in the two groups. Arousals were significantly more frequent ($P < 0.01$) in the HT than in the NT group.

Table 1. Demographic characteristics of study subjects

Variables	NT	HT	*P*
Male, %	60	38	0.64
White, %	60	67	0.16
Age, years	39 ± 3	36 ± 4	0.75
BMI, kg/m^2	23 ± 0.7	24 ± 0.3	0.43
Neck circumference, cm	35 ± 1.0	34 ± 1.1	0.74
Cardiovascular parameters			
Systolic BP, mm Hg[a]	107 ± 3.7	175 ± 6.9	< 0.01*
Diastolic BP, mm Hg[a]	70 ± 3.1	92 ± 4.8	< 0.01*
Heart rate, bpm	70 ± 1.8	75 ± 1.8	0.52

*$P < 0.05$ for differences between groups.
Values are means ± SEM.
[a]The blood pressure values correspond to the mean of two office blood pressure readings after 2 weeks of withdrawal of antihypertensive medication.
Abbreviations: BMI, body mass index; HT, hypertensive; NT, normotensive; BP, blood pressure.

Table 2. Sleep parameters of study subjects

Variables	NT	HT	*P*
ESS	6.3 ± 0.9	6.3 ± 0.2	0.96
Total sleep time, min	391 ± 19	340 ± 26	0.14
Sleep efficiency	86 ± 3.0	80 ± 5.2	0.28
Stage 1, %TST	6 ± 1	8 ± 3	0.47
Stage 2, %TST	65 ± 3	62 ± 4	0.65
Stage 3, %TST	13 ± 2	15 ± 4	0.53
REM, %TST	16 ± 1	15 ± 2	0.64
AHI, events/h	2 ± 1	2 ± 1	0.68
Minimal O_2 saturation, %	90 ± 1	91 ± 1	0.88
Overall arousals, events/h	12 ± 3	25 ± 5	0.03*
Awakenings, events/h	1 ± 0.4	2 ± 0.7	0.64

*$P < 0.05$ for differences between groups.
Values are in means ± SEM.
Abbreviations: AHI, apnea-hypopnea index; ESS, Epworth Sleepiness Score; HT, hypertensive; NT, normotensive; TST, total sleep time.

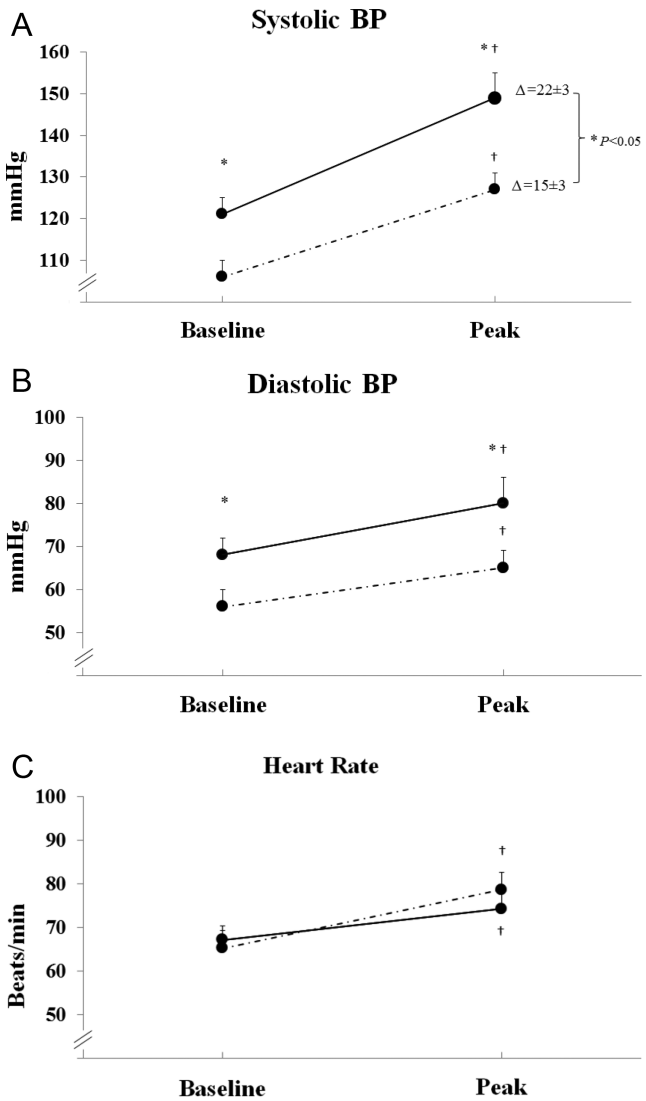

Figure 1. Systolic blood pressure (BP) (**A**), diastolic blood pressure (**B**), and heart rate (**C**) at the beginning of arousal from sleep and at the maximal (peak) response during arousal. The solid line represents the hypertensive group and the dashed line the normotensive group in the study. *P<0.05 differences between groups; †P<0.05 vs. differences within groups.

The hemodynamic data at 15 seconds before arousal from the N2 of NREM sleep was different in the HT and NT groups. The HT patients had higher systolic (125 ± 5 mm Hg vs. 104 ± 4 mm Hg, P = 0.003), diastolic (67 ± 3 mm Hg vs. 54 ± 2 mm Hg, P = 0.003), and mean BP values (87 ± 4 mm Hg vs. 71 ± 2 mm Hg, P = 0.002) than did the NT group. There were no differences in HR in the HT and NT groups during the 15 seconds before arousal (66 ± 3 bpm vs. 64 ± 2 bpm, P = 0.58, respectively).

Hemodynamic responses to arousal in normotensive and hypertensive subjects

During arousal, systolic BP, diastolic BP, and HR increased significantly over their baseline values (immediate values before arousal) in both the HT and NT groups (P < 0.05). Both the baseline systolic and diastolic BP and the systolic and diastolic BP during arousal were significantly higher in the HT than in the NT group (P < 0.05) (Figure 1A and B). No differences in HR were found at baseline or during arousal in the HT and NT groups (Figure 1C).

Further analysis showed that changes in systolic BP during arousal (maximal systolic BP value minus baseline systolic BP value) in the HT group were significantly greater than in the NT group (22 ± 3 vs. 15 ± 3 mm Hg, P < 0.05) (Figure 1A).

Neither the mean duration of arousal nor the time needed to trigger an increase in systolic BP induced by spontaneous arousals differed in the HT patients and NT subjects (Table 3). However, increased systolic BP was inversely correlated with the duration of arousal in the HT patients (r = –0.71, P < 0.05) but not in NT individuals (r = –0.014; P < 0.05) (Figure 2).

DISCUSSION

The major findings of this study are that: (i) Despite the absence of OSA and the similar overall sleep efficiency and

architecture in the HT and NT groups in the study, HT patients had on average a twofold greater the number of arousals during sleep than did the NT subjects; and (ii) the magnitude of the increase in systolic BP during spontaneous arousal during NREM sleep was significantly greater in the HT patients than in the NT subjects. Although transient, the repetitive and frequent surges in BP triggered by arousals may be clinically relevant in HT patients.

Arousal is a marker of sleep fragmentation accompanied by a sudden, transient increase in the level of vigilance or spontaneous oscillations in the level of vigilance.[20] It also represents an important physiological preparation in anticipation of rapid reaction or action when waking from sleep.[21] Although arousal may represent a physiological mechanism, it also provokes a significant increase in HR, BP,[22] ventilation,[23–25] and cerebral blood flow.[26] In some circumstances, frequent arousals may be potentially harmful. Momentary increases in muscle sympathetic nervous activity and BP associated with arousal from sleep during the N2 of NREM sleep[27] provide insights into potential mechanisms whereby arousal from sleep can contribute in part to the initiation of cardiac events. For instance, Morrell *et al.*[28] using a large population from the Wisconsin Sleep Cohort Study, found that sleep fragmentation (defined as the total number of awakenings and shifts to stage 1 sleep divided by the total sleep time) was independently associated with sustained higher levels of systolic BP in the awake state in individuals without overt sleep-disordered breathing, suggesting that repeated arousals may contribute to a sustained increase in BP. Another observational study[29] suggested a link between arousal-related transient increases in BP and daytime hypertension in a group of habitual heavy snorers without OSA. Our study extends these findings by showing that the frequency of arousals in HT patients is greater and promotes a greater BP response than in appropriate control subjects.

The hemodynamic consequence of arousals from sleep as assessed with beat-by-beat BP monitoring has been poorly understood. In healthy individuals, arousals induced by auditory tones during sleep promote abrupt hemodynamic changes, characterized by increases in BP and HR.[30,31] The simultaneous increase in HR and BP during spontaneous arousal suggests that the baroreflex is rapidly reset or overwhelmed by the arousal stimuli.[21] Furthermore, previous studies show that spontaneous arousals during NREM sleep[32] or auditory arousals from sleep consistently reduce the latency of sympathetic bursts, which may reflect attenuated baroreflex control.[33] In support of these previous findings, we have observed that spontaneous arousals abruptly induce a more prominent increase in systolic BP in HT patients than in NT subjects during the N2 of NREM sleep period. Both the NT subjects and HT patients in our study exhibited an increase in HR during arousals. The increase in HR is probably a marker of a surge in sympathetic activity that occurs in response to arousal, regardless of the BP status of the subject. Interestingly, we observed an inverse correlation between the increase in BP with arousal and the duration of arousal. It is possible that baroreflex control is impaired in HT patients during abrupt transitions from sleep to wakefulness. This finding should be explored in further investigations.

Table 3. Duration of electroencephalographic arousal and time taken to initiate and reach peak systolic blood pressure responses following onset of arousal in study subjects

Variables	NT	HT	*P*
Time to initiate response, seconds	0.47 ± 0.1	0.51 ± 0.1	0.67
Time to reach peak response, seconds	5.9 ± 0.6	6.1 ± 0.6	0.86
Electroencephalographic duration of arousal, seconds	9.8 ± 0.4	9.5 ± 0.6	0.64
Duration of arousal minus time to beginning of response, seconds	9.4 ± 0.4	9.0 ± 0.6	0.61

Values are in means ± SEM.

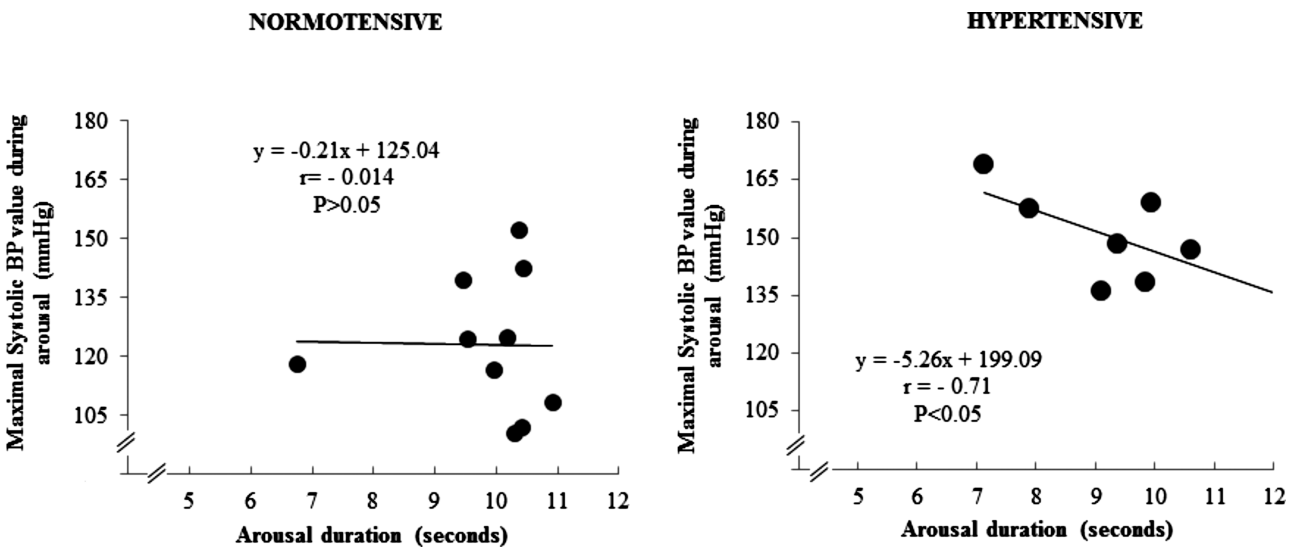

Figure 2. Relationship between systolic blood pressure (BP) and duration of arousal in normotensive and hypertensive study groups.

The present study was not designed to explore the potential mechanisms by which hypertension can promote sleep disruption in humans. However, recent experimental data have shown that spontaneously HT rats have more frequent interruptions during quiet sleep[34] than do NT rats. Interestingly, sleep interruptions in spontaneously HT rats occurred in parallel to surges in sympathetic activity.[35] In addition, an alpha-1-adrenergic antagonist reversed, at least partly, the poor sleep quality of spontaneously HT rats, suggesting that exacerbated sympathetic activation is a main mechanism linking hypertension and sleep fragmentation. It has been reported that norepinephrine is one of the main neurotransmitters in the monoaminergic arousal system and is prominently implicated in arousal and waking in conjunction with the cholinergic system and orexinergic neurons.[36–38] In addition, it is possible that HT patients have not only a poorer quality of sleep but also a shorter sleep time than do NT individuals. In the present study, the HT group had a mean sleep time that was almost 1 hour shorter than that of the NT group. Although this difference was not significant, this lack of significance most likely reflects the small sample size in the study.

Our study has some strengths and limitations that should be addressed. A strength of our study was the simultaneous availability of polysomnographic data and data from hemodynamic monitoring during sleep. In addition, we selected the study patients and controls carefully. In particular, we performed screening tests to exclude secondary forms of hypertension (including OSA) in the HT patients. We also carefully withdrew medications 2 weeks before the experiments in our study to exclude the confounding effects of antihypertensive drugs.[39] The limitations of the study included: (i) Its small sample size, which may have contributed to the lack of a difference in the baseline characteristics of the study groups in terms of gender, and the lack of a difference in the sleep duration. We would like to emphasize that our sample size was limited by the criteria for inclusion/exclusion of study subjects, including withdrawal from drugs and measurement of beat-by-beat BP during full-night polysomnography, which requires constant monitoring of the device used for measurement of BP. (ii) The use of noninvasive methods to determine BP during sleep. However, the Portapres is a validated system for the continuous measurement of BP,[17] and can be used in individuals under stable conditions; (iii) Our analysis was limited to the N2 of NREM sleep. However, the N2 is the most common phase of sleep (> 60% of total sleep). (iii) To avoid potentially excessive monitoring during sleep, we did not perform 24-hour ambulatory BP monitoring of our subjects. We therefore cannot ignore the possibility that some of the HT patients in our study would have had a non-dipping pattern of BP.

In conclusion, the present study suggests that HT patients have more sleep fragmentation and a significantly higher systolic BP surge during spontaneous arousals than do NT individuals. Although sleep fragmentation may at least in theory be explained by a hyperadrenergic state, the exacerbated BP response on arousal of patients with hypertension may reflect an impaired autonomic nervous regulatory process observed in HT patients. These findings may partly explain the major risk of morbidity attributed to a surge in night-time BP in HT patients observed in epidemiological studies done with 24-hour BP monitoring. Further studies are necessary to elucidate potential pathways for night-time surges in BP in primary hypertension and to determine whether a chronotropic approach to the treatment of such hypertension or nonpharmacological interventions will reduce sleep fragmentation and surges in BP during sleep in individuals with primary hypertension.

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DISCLOSURE

The authors have no conflicts of interest to declare.

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