Nocturnal blood pressure profiles among normotensive, controlled hypertensive and refractory hypertensive subjects

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BACKGROUND: Nocturnal blood pressure abnormalities are independently associated with an increased risk of death and cardiovascular disease. It is unclear, however, whether they are related to the presence or severity of hypertension.

OBJECTIVES: To determine and compare the prevalence of sleep pattern disturbances in normotensive (NT) and hypertensive patients.

METHODS: The present cross-sectional study assessed the nocturnal blood pressure profiles from 24 h ambulatory blood pressure monitoring of refractory hypertensive (RH) (n=26), controlled hypertensive (CH) (n=52) and NT (n=52) subjects who were matched for age, sex and body mass index. Results are expressed as mean $\pm$ SD or proportion, as appropriate.

RESULTS: During sleep, the percentage fall in mean arterial pressure was $15.1 \pm 6.1\%$ in the NT group, $11.5 \pm 7.0\%$ in the CH group and $7.7 \pm 7.7\%$ in the RH group ($P < 0.0001$). The corresponding proportions of nondipping were 25.0%, 42.3% and 61.5%, respectively ($P = 0.006$), and those of nocturnal hypertension were 9.6%, 23.1% and 84.6%, respectively ($P < 0.0001$). All pairwise comparisons of nocturnal blood pressure fall were significant. The proportion of subjects in the RH group who experienced a rise in nocturnal blood pressure (19.2%) was significantly greater than the proportions in the NT and CH groups ($P = 0.001$), as was the proportion of subjects with nocturnal hypertension ($P < 0.0001$). There was less extreme dipping in RH, although the difference was not statistically significant ($P = 0.08$).

CONCLUSIONS: A significantly higher prevalence of nondipping, nocturnal hypertension and nocturnal blood pressure rising in RH was demonstrated. These sleep disturbances or independently, their cause, may account for the difficulties in attaining blood pressure control.

Key Words: Ambulatory blood pressure monitoring; Nocturnal blood pressure; Refractory hypertension

Refractory hypertension (RH) is emerging as a significant and growing problem in managing hypertension. In a previous study (1), 11% of patients referred for uncontrolled hypertension were found to meet the criteria for RH. Not surprisingly, RH is associated with an increased risk of hypertensive target organ damage (2). Experts recommend 24 h ambulatory blood pressure monitoring (ABPM) to differentiate true RH from white-coat resistant hypertension (3). The test also provides information on nocturnal blood pressure (BP) and the means to assess its relationship with survival and the occurrence of cardiovascular and renal events, adjusted for daytime or 24 h BP (4-12). Several sleep BP pattern disturbances in normotensive (NT) and hypertensive subjects have been identified. A Japanese study (6) found a 20% increase in cardiovascular mortality for every 5% attenuation in nocturnal BP fall, independent of

Les profils de tension artérielle nocturne chez des sujets hypertendus contrôlés et réfractaires

HISTORIQUE : Les anomalies de la tension artérielle nocturne s'associent de façon indépendante à une augmentation du risque de décès et de maladie cardiovasculaire. Cependant, il n'est pas établi clairement si elles sont liées à la présence ou à la gravité de l'hypertension.

OBJECTIFS : Déterminer et comparer la prévalence des perturbations des structures du sommeil chez les patients normotendus (NT) et hypertendus.

MÉTHODOLOGIE : La présente étude transversale visait à évaluer les profils de tension artérielle nocturne à partir de la surveillance de la tension artérielle ambulatoire pendant 24 heures chez des sujets hypertendus réfractaires (HR, n=26), des sujets hypertendus contrôlés (HC, n=52) et des sujets NT (n=52) appariés selon l'âge, le sexe et l'indice de masse corporelle. Les résultats sont exprimés à titre de moyenne $\pm$ ÉT ou de proportion, selon le cas.

RÉSULTATS : Pendant le sommeil, la chute de tension artérielle en pourcentage était de $15,1 \pm 6,1\%$ dans le groupe NT, de $11,5 \pm 7,0\%$ dans le groupe HC et de $7,7 \pm 7,7\%$ dans le groupe HR ($P < 0,0001$). Les proportions correspondantes d'absence de chute étaient de 25,0 %, de 42,3 % et de 61,5 %, respectivement ($P = 0,006$) et celles d'hypertension nocturne de 9,6 %, de 23,1 % et de 84,6 %, respectivement ($P < 0,0001$). Toutes les comparaisons de chute de tension artérielle nocturne par paire étaient significatives. La proportion de sujets du groupe HR qui avaient subi une augmentation de leur tension artérielle nocturne (19,2 %) était considérablement plus importante que celle des groupes NT et HC ($P = 0,001$), tout comme la proportion de sujets faisant de l'hypertension nocturne ($P < 0,0001$). Les chutes étaient moins extrêmes chez les HR, mais la différence n'était pas statistiquement significative ($P = 0,08$).

CONCLUSIONS : On a démontré une prévalence considérablement élevée d'absence de chutes, d'hypertension nocturne et d'augmentation de la tension artérielle nocturne chez les HR. Ces perturbations du sommeil ou, indépendamment, leur cause, peuvent expliquer la difficulté à parvenir au contrôle de la tension artérielle.

overall 24 h BP. In another study (13), a J-shaped curve of stroke incidence was found among extreme dippers (subjects with a 20% or greater fall in nocturnal BP) and nondippers, albeit from different causes, with risers (subjects with a paradoxical increase in nocturnal BP) having the worst cardiovascular prognosis. Recently, nighttime BP, independent of daytime level, was found to be a predictor of death and cardiovascular disease (12). Surprisingly, to date, little attention has been given to sleep BP patterns in subjects with RH, and the results in the existing literature conflict, at least in part, with the use of different definitions of the condition itself and methods to define the nighttime period (14-17).

The present study was undertaken to determine whether sleep BP pattern disturbances are related to the presence or severity of hypertension. We used a widely accepted definition of RH and diaries

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to ascertain the nighttime period to overcome shortcomings of some earlier studies (18).

METHODS

Study design

A cross-sectional study design was used to compare the sleep BP patterns of NT and hypertensive subjects, individually matched for age, sex and body mass index (BMI). The present study was approved by the Research Ethics Board of Mount Sinai Hospital (Toronto, Ontario).

Subjects

Patients with RH were previously identified through chart review in the Mount Sinai Hospital hypertension clinic, in which an evaluation to ascertain the causes of apparent resistance to medical therapy was conducted. RH was defined as a daytime BP of 135/85 mmHg or higher on ABPM while adherent to three or more antihypertensive medications at maximal or near-maximal doses including a diuretic, unless contraindicated or intolerant (eg, hyponatremia) (19). Patients were excluded if they were noncompliant with antihypertensive medication (self-report [20]), had an underlying correctable secondary form of hypertension, chronic kidney disease defined as a body surface area-adjusted creatinine clearance of less than 45 mL/min/1.73 m², ingestion of exogenous substances that can raise BP or a history of alcohol abuse (21). Controlled hypertension (CH) was defined as a daytime BP of lower than 135/85 mmHg on ABPM while on three or fewer antihypertensive medications (19). NT was defined as a daytime BP of lower than 135/85 mmHg on ABPM while on no antihypertensive medications. The latter two groups of patients were then matched for age (± 10 years), sex and BMI (± 5 kg/m²) to the patients with RH in a 2:1 ratio. In defining the number of antihypertensive medications, dihydropyridine and nondihydropyridine calcium channel blockers were considered to be two drugs, as were diuretics with actions on different nephron sites. Diabetes status was determined via medication review (prescription for oral hypoglycemic agent or insulin).

ABPM

ABPM was performed for 24 h starting at the same time of a regular working day in all patients following their usual prescribing pattern for those on antihypertensive medications using an automated sphygmomanometer (SL-90207; Spacelabs Medical Inc, USA). An appropriately sized cuff was fitted to the nondominant arm, and BP was measured every 20 min during the wake period and every 30 min during the sleep period. Patients recorded the times when they retired at night and awoke in the morning; such times were then rounded to the nearest hour. The formula:

$$2/3 \times \text{diastolic BP} + 1/3 \times \text{systolic BP}$$

was used to calculate mean arterial pressure. The 24 h BP was determined using the following formula:

$$\frac{\text{proportion of 24 h awake} \times \text{daytime BP} + \text{proportion of 24 h asleep} \times \text{nighttime BP}}$$

The nocturnal BP fall was defined as the degree of fall (%) in nocturnal mean arterial pressure relative to the diurnal mean arterial pressure:

$$100 \times (1 - [\text{nighttime mean arterial pressure} \div \text{daytime mean arterial pressure}])$$

The nocturnal BP profile was also assessed in three other ways (dipping status, nocturnal BP status and nocturnal BP pattern) to reflect the various, albeit related, measures reported in the literature. Dipping status was expressed as either dipper or nondipper, with dipping defined as a 10% or greater nighttime fall in mean arterial pressure relative to its daytime value. Nocturnal BP status was expressed as either nocturnal normotension or hypertension, with nocturnal hypertension defined as a nighttime BP of 125/75 mmHg or greater (18). Four nocturnal BP

patterns were defined based on the percentage change in nocturnal mean arterial pressure: extreme dipping (20% or greater fall), normal dipping (10% or greater but less than 20% fall), attenuated dipping (0% or greater but less than 10% fall) or rising (less than 0% fall). Analyses were then repeated using systolic and diastolic BP.

Statistical analysis

A sample size of 21 per group was calculated, assuming nocturnal BP falls of 15% (NT) (22), 12% (CH) (16) and 9% (RH) (16), a pooled SD of 6% and equal group sizes (two-tailed alpha = 0.05, power = 0.8). Assuming nondipper proportions of 13% (NT) (22), 50% (CH) (16) and 69% (RH) (16), and equal group sizes (two-tailed alpha = 0.05, power = 0.8), sample sizes were calculated to be 11 per group (NT versus RH) and 80 per group (CH versus RH) (23). Continuous variables were expressed as mean values along with SDs. Categorical variables were described as proportions. Although the groups were matched, one-way ANOVA (Neuman-Keuls post hoc test) was used for continuous variables. The unpaired *t* test was used to compare the number of antihypertensive drugs between the two hypertensive groups. Pearson's χ^2 or Fisher's exact tests were used, as appropriate, to evaluate categorical variables followed by decomposition, where indicated (24). ANCOVA (for nocturnal BP fall) and logistic regression (for nondipping and nocturnal hypertension) were also enlisted to determine whether the associations between BP status and the above parenthesized outcomes were independent of diabetic status. A two-tailed *P* < 0.05 was considered to be statistically significant. All analyses were conducted using SAS Version 9.1.3 (SAS Institute, USA).

RESULTS

Baseline characteristics (Table 1)

A total of 46 eligible subjects with RH were identified (mean [$\pm$ SD] age 59.7 $\pm$ 10.9 years, BMI 33.1 $\pm$ 6.3 kg/m², 60.9% men, 19.6% diabetic). Of these, 26 were successfully individually matched with 52 subjects with NT and 52 subjects with CH. The groups were, therefore, similar with respect to age, sex and BMI, with higher daytime, nighttime and 24 h BP values in the RH group, along with a greater number of antihypertensive drugs (*P* < 0.0001). The mean serum creatinine among subjects with RH was 89.0 $\pm$ 21.5 μ mol/L.

Nocturnal BP profiles (Table 2)

During sleep, the percentage fall in nocturnal mean arterial pressure was 8.4 $\pm$ 7.2% and the proportions of nondippers and subjects with nocturnal hypertension were 58.7% and 84.8%, respectively, in the RH group (*n*=46) as a whole. The proportions of extreme dippers, attenuated dippers and risers were 4.4%, 37.0% and 15.2%, respectively. Following matching, the percentage fall in nocturnal mean arterial pressure was 15.1 $\pm$ 6.1% in the NT group, 11.5 $\pm$ 7.0% in the CH group and 7.7 $\pm$ 7.7% in the RH group (*P* < 0.0001). All pairwise comparisons were significant. The nondipper proportions were 25.0% in the NT group, 42.3% in the CH group and 61.5% in the RH group (*P* = 0.006). Deconstruction revealed significantly more nondippers among subjects with RH compared with NT (*P* = 0.003); other pairwise comparisons were not statistically significant. The proportions for nocturnal hypertension were 9.6% in the NT group, 23.1% in the CH group and 84.6% in the RH group (*P* < 0.0001). Deconstruction revealed significantly more nocturnal hypertension among subjects with RH than among those with NT and CH (*P* < 0.0001); the remaining pairwise comparison was not statistically significant. In analyses that adjusted for diabetes status, the effect sizes observed for nocturnal BP fall, nondipping and nocturnal hypertension remained unchanged (data not shown). The proportions of extreme dippers, attenuated dippers and risers were 19.2%, 25.0% and 0% in the NT group, 17.3%, 40.4% and 1.9% in the CH group, and 3.9%, 42.3% and 19.2% in the RH group, respectively (*P* = 0.003). Deconstruction revealed significantly more risers among subjects with RH than among those with NT and CH (*P* = 0.001); conversely, the proportion of extreme dippers was smaller, although this did not reach statistical significance (*P* = 0.08).

TABLE 1
Characteristics of the normotensive, controlled hypertensive and refractory hypertensive subjects

	Normotension (n=52)	Controlled hypertension (n=52)	Refractory hypertension (n=26)	P
Age, years	56.5±11.5	58.3±11.7	57.8±10.1	0.7
BMI, kg/m ²	29.0±4.9	29.4±4.9	30.4±4.6	0.5
Male sex, %	46.1	46.1	46.1	N/A
Diabetes, %	5.8	9.6	15.4	0.33
Drug(s), n	N/A	1.7±0.7	3.8±0.9	<0.0001
ACEI, %		44.2	53.9	0.48
ARB, %		15.4	11.5	0.74
BB, %		36.5	69.2	0.008
CCB, %		32.7	84.6	<0.0001
Diuretic, %		42.3	80.8	0.002
AB, %		1.9	23.1	0.005
CS, %		0	15.4	0.01
VD, %		0	3.8	0.33
Daytime SBP, mmHg	126.5±6.4	124.9±7.0	151.1±16.7	<0.0001* 0.38†
Daytime DBP, mmHg	78.0±5.6	74.2±7.4	89.5±10.7	<0.0001* 0.01†
Daytime MAP, mmHg	94.2±5.1	91.1±6.0	110.1±10.8	<0.0001* 0.02†
Nighttime SBP, mmHg	110.2±8.1	112.6±10.6	143.0±23.7	<0.0001* 0.37†
Nighttime DBP, mmHg	64.6±6.3	64.5±8.3	80.9±11.9	<0.0001* 0.95†
Nighttime MAP, mmHg	79.8±6.2	80.5±7.9	101.6±13.9	<0.0001* 0.68†
24 h mean SBP, mmHg	122.0±6.2	122.0±7.3	149.4±17.8	<0.0001* 0.98†
24 h mean DBP, mmHg	74.5±5.2	72.1±7.3	87.6±10.8	<0.0001* 0.10†
24 h MAP, mmHg	90.3±4.7	88.7±6.0	108.2±11.1	<0.0001* 0.24†

Data presented as mean ± SD unless otherwise indicated. *Normotensive or controlled hypertensive versus refractory hypertensive subjects; †Normotensive versus controlled hypertensive subjects. AB Alpha-blocker; ACEI Angiotensin-converting enzyme inhibitor; ARB Angiotensin receptor blocker; BB Beta-blocker; BMI Body mass index; CCB Calcium channel blocker; CS Central sympatholytic; DBP Diastolic blood pressure; MAP Mean arterial pressure; N/A Not applicable; SBP Systolic blood pressure; VD Vasodilator

Analyses using systolic and diastolic BP generated equivalent results. For systolic BP, percentage nocturnal BP falls and nondipper proportions were 12.8±5.7% and 28.8% (NT), 9.9±6.0% and 51.9% (CH), and 5.6±8.7% and 69.2% (RH), respectively; for diastolic BP, 17.0±6.8% and 13.5% (NT), 12.9±8.1% and 34.6% (CH), and 9.5±7.4% and 42.3% (RH), respectively.

DISCUSSION

The present cross-sectional study demonstrated that patients with RH manifested a smaller fall in nocturnal mean arterial pressure and had a higher proportion of nondippers, nocturnal hypertension and paradoxical rise in nocturnal BP than those with CH and NT. Not surprisingly, nocturnal hypertension was the most common abnormality, being found in 85% of RH patients. There is a growing body of literature indicating that nighttime ambulatory BP is a better predictor of death and cardiovascular disease than daytime ambulatory BP readings in hypertensive patients (8,11,12) and may be a more consistent predictor of outcomes than the night-day BP ratio (4,7,11).

TABLE 2
Nocturnal blood pressure profiles of the normotensive, controlled hypertensive and refractory hypertensive subjects

	Normotension	Controlled hypertension	Refractory hypertension	P
Percentage fall in nocturnal blood pressure, %*	15.1±6.1	11.5±7.0	7.7±7.7	0.008† <0.0001‡ 0.02§
Nondipper proportion, %	25.00	42.30	61.50	0.10† 0.003‡ 0.15§
Nocturnal hypertensive proportion, %	9.60	23.10	84.60	0.11† <0.0001‡ <0.0001§

*Data presented as mean ± SD; †Normotensive versus controlled hypertensive subjects; ‡Normotensive versus refractory hypertensive subjects; §Controlled hypertensive versus refractory hypertensive subjects

Other studies have reported similar results, although none determined and compared the nocturnal BP patterns and prevalence of nocturnal hypertension in the three different groups evaluated in the present study. In a study (22) of 62 healthy middle-aged men, the percentage fall in nocturnal mean arterial pressure was 15% and the proportion of nondippers was 13%. Using a standard definition of RH in a study of 313 such patients, Muxfeldt et al (17) found that the percentage fall in nocturnal systolic and diastolic BP was 7% and 10.5%, respectively, and the proportion of nondippers was 65.8%. However, 63% of the 184 white-coat resistant hypertensive patients in this study also had a nondipping pattern. The results of an earlier and smaller study by the same group were similar except for the proportion of nondippers among white-coat resistant hypertensive patients, which was significantly lower at 49.6% (16).

Findings of several other studies differed from our own. Two cross-sectional studies (25,26) revealed that although the absolute nocturnal BP was higher in hypertensive than in NT subjects, the magnitude of and percentage decline in nocturnal BP positively correlated with daytime BP. In another study (27), hyperkinetic borderline hypertensive subjects were found to have a greater night-to-day BP gradient than NT subjects, and a similar trend was observed in normokinetic borderline hypertensive individuals. Pickering et al (28) demonstrated an identical circadian BP profile in hypertensive and NT individuals. A study (14) of RH patients found no differences in the night to day BP ratio among subjects with an office diastolic BP higher than 100 mmHg when stratified into tertiles according to daytime diastolic BP. Similarly, another RH study (15) found an equivalent fall in nocturnal BP in patients with RH and white-coat resistant hypertension, and the percentage of nondippers in the true RH group was only 27% compared with 61.5% in our study. There are several possible explanations for these disparate results including the use of fixed time intervals rather than diaries to identify the daytime and nighttime periods, and differing definitions of RH. White-coat resistant hypertensive patients as a comparator group may not be identical to our CH patients. Finally, we used a matching strategy before data analysis to control for the potential confounding effects of age, sex and BMI. Of note, in the present analysis, we did not include patients with a daytime BP lower than 135/85 mmHg on ABPM but requiring four or more antihypertensive medications. According to a recently published consensus paper (19), such patients with 'controlled RH' are still considered to be resistant to treatment. Whether their nocturnal BP profiles are similar to individuals with RH or CH remains unknown.

The mechanism(s) accounting for the association of RH with nondipping, nocturnal hypertension and rising of nocturnal BP remains speculative. Several possibilities exist including an underlying

abnormal nocturnal sympathovagal balance (29-31) and occult fluid retention (32), among others (33). Salt-sensitive hypertension is associated with the phenomenon of nondipping (34) and interventions that reduce total body sodium balance in salt-sensitive individuals restore the normal nocturnal dipping pattern (35,36). These findings suggest that excess extracellular fluid volume may be causally related. Consistent with this suggestion are the parallel observations of greater attenuation of the normal nocturnal dipping pattern in our study and a higher prevalence of salt sensitivity in hypertensive than in NT subjects (37). Other observations suggest that occult volume expansion may be a dominant feature accounting for apparent treatment resistance in RH patients (38,39). For example, in a three-month interventional trial of drug-resistant hypertension, patients randomly assigned to receive antihypertensive treatment dictated by noninvasive hemodynamic measurements had significantly lower BP and better BP control than those receiving specialist care alone, and the differences were attributed to a significantly higher final diuretic dosing (39).

Our study is limited by its observational nature and the always-present problem of confounding variables. Despite matching for age, sex and BMI, there may have been an uneven distribution of other potential confounding factors associated with salt sensitivity and/or nondipping status (eg, African-American ethnicity, diabetes, chronic kidney disease, poor sleep quality or quantity, sleep-disordered breathing or dietary potassium intake) (37,40-42,29), and alterations in daytime or nighttime BP (eg, nocturnal body position, diurnal activity) (29,43). Importantly herein, sleep-disordered breathing, particularly obstructive sleep apnea-hypopnea, has been strongly associated with both nondipping and RH (44); this raises the very real possibility that the observed association among nocturnal hypertension, the nondipping pattern and RH merely reflects recurrent upper airway obstruction and BP surges occurring throughout sleep. It is unlikely that a significant subset of subjects with RH suffered from chronic kidney disease because the estimated mean body surface area-adjusted creatinine clearance was 81.5 ± 19.6 mL/min/1.73 m². Furthermore, possible inclusion of chronic kidney disease among subjects with CH and NT would bias toward a more conservative estimate. Although antihypertensive drug

prescriptions were elucidated among the patients with CH and RH, the timing of administration was not; conversion from nondipper or riser to dipper status with nighttime dosing of antihypertensive agents has been demonstrated in some studies (45-47). Data also suggest that, despite equivalent daytime BP control, various antihypertensive medications may exert differential effects on nighttime BP (48).

There are several shortfalls with respect to ascertainment of dipping status, particularly given the greater dependency of this measure on nocturnal BP readings (45,29). First, we did not account for nocturnal awakenings in determining the average nighttime BP (nor did we account for naps during the day in determining average daytime BP), which could result in misclassification (49,50). Second, nighttime BP was determined using each subject's reported bedtime as opposed to polysomnographically verified sleep time or on the basis of an arbitrarily fixed clock time. However, our operating definition was applied throughout the study and all definitions appear to be adequately reliable (51). Third, because dipping is defined by a difference score, its reproducibility falls short of the individual daytime and nighttime BP levels (29,52,53); on repeated ABPM, agreement in diagnosing nocturnal hypertension on the basis of the two measurements was greater using an absolute nocturnal BP cut-off rather than the percentage nocturnal BP fall (54). Also, one would anticipate a regression to the mean effect had we repeated measurements.

Overall, our cross-sectional study, in agreement with the findings of some (16,17) but not all investigators (14,15), demonstrates that nondipping is a common finding in patients with RH. The novel findings of our study are the extraordinarily high prevalence of nocturnal hypertension and the increased prevalence of nocturnal BP rising (and a trend toward less extreme dipping) in subjects with RH. While the nature of these circadian disturbances remains undetermined, we postulate that it may reflect an underlying abnormality (eg, covert volume overload or obstructive sleep apnea-hypopnea) that also accounts for the challenges in attaining BP control in RH.

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