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Identifying patterns of diurnal blood pressure variation among ELSA-Brasil participants

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Abstract

Ambulatory blood pressure monitoring (ABPM) is the gold standard method for the diagnosis of hypertension. ABPM provides a set of repeated measurements for blood pressure (BP), usually over 24 h. Traditional approaches characterize diurnal BP variation by single ABPM parameters such as average and standard deviation, regardless of the temporal nature of the data. In this way, information about the pattern of diurnal BP variation and relationship between parameters is lost. The objective of this study was to identify and characterize daily BP patterns considering the set of repeated measures from 24-h ABPM. A total of 859 adult participants of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) performed a 24-h ABPM record. Hypertension, sex, age, race/color, education, marital status, smoking, alcohol, physical activity, and BMI were the covariables analyzed. Techniques for longitudinal clustering, multinomial models, and models with mixed effects were used. Three daily BP patterns were identified. Daily BP patterns with high BP presented higher standard deviation and morning surge and lower nocturnal dipping. They showed greater systolic BP variability and faster rise than fall in diastolic BP during sleep. Hypertensive, "pardos," and men had greater odds to present these patterns. Daily BP patterns with high BP presented the worst profile concerning ABPM parameters associated with cardiovascular risk. The daily BP patterns identified contribute to the characterization of diurnal BP variation.

1 | INTRODUCTION

Noncommunicable diseases are the leading cause of death in the world, and the majority of these deaths occur due to cardiovascular diseases.[1,2] Ambulatory blood pressure monitoring (ABPM) is recommended as the gold standard method for the diagnosis of hypertension. Moreover, ABPM gives a more accurate assessment of cardiovascular risk than blood pressure (BP) levels obtained by the traditional office measurements.[3,4]

Daytime, nighttime, and 24-h average are among the most important ABPM parameters in clinical practice, related to the diagnosis of hypertension.[5-8] The fall in nighttime BP average, compared to the daytime average, defined as nocturnal dipping, is an established predictor of cardiovascular events.[5,7-11] In particular, the nondipping

pattern (<10%) is related to an increased risk for cardiovascular events compared to the dipping pattern (from 10% to 20%).[12-14] Morning surge and average real variability (ARV) are ABPM parameters that have been defined most recently. Studies have shown the relationship between these parameters and cardiovascular events.[15-17] However, the inexistence of consolidated thresholds in the literature makes it difficult to use them in clinical practice.

Despite the importance of ABPM parameters and their relationship to cardiovascular events, a lot of information is lost by characterizing diurnal BP variation by single values. For example, the joint effect of ABPM parameters on risk estimation is still an open question. Dependence between parameters is an important component and neglecting it can lead to a wrong idea about the impact of ABPM parameters on the increased risk for cardiovascular events. One way to address this problem is to identify daily BP patterns related to a higher risk for cardiovascular events. Moreover, the study of diurnal BP variation and periods of the day that mark the daily variability is particularly important in monitoring the therapeutic response of hypertensive patients in 24 h.

Ambulatory blood pressure monitoring parameters are associated with biological, behavioral, and social factors.[9,18] Studies report that individual characteristics such as age, race, sex, obesity, and socioeconomic status are associated with ARV, nocturnal dipping, and morning surge,[10,11,19,20] but the impact of individual factors on diurnal BP variation, composed of multiple repeated measurements, is still unknown.

Ambulatory blood pressure monitoring recordings provide repeated BP measurements, usually over a 24-h period. By using single values to characterize complete variation over 24 h, information about the evolution pattern, intrinsic variability dynamics, and relations between ABPM parameters is lost. Moreover, periods of day which are markers of daily BP variability may be overlooked when reducing to point values. Identifying and characterizing daily BP patterns, considering the set of repeated measures from 24-h ABPM, is the new approach of this study to the characterization of diurnal BP variation.

2 | METHODS

2.1 | Design and study population

ELSA-Brasil is a multicenter cohort study conducted in six Brazilian cities. Data collection at baseline (first wave) was performed from 2008 to 2010 with a total of 15 105 active or retired civil servants (35-74 years) enrolled. The second wave (2012-2014) had a 7% follow-up loss, remaining a total of 14 014 participants. In each wave, participants were submitted to a set of clinical, laboratory, and imaging examinations, in addition to measurements and a detailed personal interview by trained personnel. The study design and sampling procedures of ELSA-Brasil have been reported previously.[21,22]

Concomitantly to the second wave of data collection, the participants of ELSA-Brasil in Rio de Janeiro Center, regardless of the BP measured or the use of antihypertensives, were invited to be part of a supplementary study to record the 24-h ABPM. Data collection occurred on a subsequent visit, between January 2013 and December 2014, and the final sample was 859 participants. Retirees and shift workers were not included in this supplementary study.

After instructions, the ABPM device (Spacelabs 90207) was placed in the non-dominant arm, using an appropriate cuff size, in order not to interfere in the usual activities of the participants. The device was placed in the workplace, near the arrival time of each participant, and was programmed to obtain readings every 20 min up to 11 p.m. and from 11 p.m. to 6 a.m. every 30 min.[7,8,23,24] Participants who had <16 valid measurements at daytime and/or eight valid measurements at nighttime were excluded.[8] Individuals were instructed to maintain a routine and keep diaries with periods of activities and medications and were asked to avoid performing physical leisure activities and drinking alcoholic beverages.

ELSA-Brasil was approved by the National Research Ethics Committee (Conep—No. 13065), and the research protocol developed at the RJ Research Centre, including the supplementary study, was approved by the Research Ethics Committee of the Oswaldo Cruz Institute (CEP Fiocruz/IOC—No. 343/06). All participants gave written consent to participate.

2.2 | Study variables

2.2.1 | Hypertension and antihypertensives

During the clinic visit, BP was measured three times after 5 min of rest in a seated position in a quiet room at controlled temperature (20-24°C), using a validated monitor (Omron HEM 705CPINT).[24,25] BP was considered as the average of the second and third measurements.[24] Participants were asked about any drug use. Antihypertensive drugs were characterized according to their pharmacological action into seven categories: diuretics (thiazides, loop diuretics, aldosterone antagonists, and potassium-sparing drugs); beta-blockers; calcium-channel blockers; angiotensin-converting enzyme (ACE) inhibitors; angiotensin II antagonists; vasodilators (direct action); and central and peripheral sympatholytics. The presence of hypertension was based on systolic BP ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg and/or antihypertensive treatment.[26]

2.2.2 | ABPM parameters

The ABPM parameters were as follows: averages and standard deviation (24 h, daytime, and nighttime), ARV (mm Hg—the average of absolute changes between consecutive BP readings),[15,16] BP velocity (mm Hg/h—defined by the rate of change of BP by time interval), nocturnal dipping (1 minus the ratio of the mean sleep BP by the mean awake BP—nondippers: <10%; dippers: ≥10%),[7] sleep-through

morning surge (mm Hg—the difference between the morning BP: the average of the first 2 h upon awakening, and the lowest BP value during the sleep: average between the lowest reading plus the readings immediately before and after), and preawakening morning surge (mm Hg—the difference between the morning BP and the average of values recorded in the 2 h before waking up).[17] The selection of the daytime and nighttime intervals was based on the times reported by the participants in their diaries.

2.2.3 | Covariates

The following covariates were included in the analysis, considering BP relationships: sex (male and female); age (continuous, in years); education (secondary, undergraduate and postgraduate); self-reported race/color (based on Brazilian Census classification: white, "pardo," and black; indigenous and Asian were excluded due to the low frequency observed [*N* = 32]); marital status (single or not single) [27]; smoking (never, past, or current)[21,28]; consumption of alcohol (not consuming, moderate—consumption <210 and <140 g/wk for men and women, respectively, excessive—higher than previous consumption limits) [29,30]; physical activity in leisure time (weak, moderate, and strong following the classification of the International Physical Activity Questionnaire, in the domain of leisure time physical activity)[27,28]; and body mass index (BMI) (eutrophic = BMI < 25; overweight BMI ≥ 25 to <30; obese ≥30 kg/m^2).[28]

2.3 | Statistical analysis

Clustering longitudinal data were used to find daily BP patterns. In general, clustering techniques aim to divide the population into homogeneous subgroups based on the similarity between individuals.[31] Regarding longitudinal data, there are different clustering methods based on different concepts of similarity (usually distance), most of them consider similar individuals when in each time point they have close trajectories.[32-34] The disadvantage of these techniques is that they are based on local proximity and may not capture similar but time-shifted trajectories. ABPM is commonly unbalanced and time-shifted data; therefore, these techniques are not suitable for ABPM clustering. In this study, Frechét distance was used, a shape-respecting distance that considers similar individuals when they have trajectories with similar shapes.[33,35] The Ramer-Douglas-Peucker algorithm (RDPa) was used for reducing the number of points in trajectories only for the clustering construction.[33,35] Average silhouette method was used to determine the number of clusters (Appendix S1). Descriptive analysis was performed, and ABPM parameters were estimated for each cluster. Differences among the clusters were tested by Pearson's chi-square test, analysis of variance, and Kruskal-Wallis test.

Multinomial models were fitted to identify individual factors associated with the daily BP patterns, and the stepwise method was used. Mixed linear models were fitted for each cluster to estimate the BP velocity in each period of the day, by using piecewise linear splines. Five periods of the day were analyzed: work, home, sleep1 (first sleep reading to lowest sleep reading), sleep2 (lowest sleep reading until last sleep reading), and morning, according to the times reported by the participants. The likelihood ratio test was used to compare the models and correlation structure. The AR1 correlation structure presented a better fit. Variability markers of diurnal BP variation were identified by the BP velocity estimators at each period of the day. All analysis was performed for both systolic BP and diastolic BP. The level of significance was set at $p < .05$. The R 3.5.0 software was used in all analyses.

3 | RESULTS

From the 859 participants with ABPM records, 77 were excluded from the analysis (45 with <16 valid measures in the daytime and/or eight measures in the nighttime period and 32 indigenous or asiatics). Among the 782 participants included, almost equally divided by sex (50.2% male, 49.8% female), the average age was 51.3 years with range of 38-69 years; 332 (42.4%) were hypertensive; 450 (57.5%) white, 235 (30.1%) "pardo," and 97 (12.4%) black; 332 (42.4%) overweight and 210 (26.9%) obese; 372 (47.6%) postgraduate and 248 (31.7%) undergraduate; 535 (68.4%) not single; 484 (61.9%) have never smoked and 215 (27.5%) have smoked; 379 (48.5%) not consuming alcohol and 300 (38.4%) consume moderately; and 562 (71.9%) were engaged in weak and 140 (17.9%) in moderate physical activity.

The average systolic BP in 24 h was 124.7 mm Hg, while the diastolic BP was 78.8 mm Hg (Table 1). The average daytime was greater than nighttime for both BP (daytime—systolic: 128.6 mm Hg; diastolic: 82.4 mm Hg; nighttime—systolic: 112.8 mm Hg; diastolic: 67.9 mm Hg). The standard deviation observed in systolic BP was greater during the daytime than at nighttime (9.4 and 8.7 mm Hg, respectively), while for diastolic BP, there was almost no difference (7.6 and 7.8 mm Hg, respectively). BP velocity was higher during the daytime than at nighttime for both BP (daytime—systolic: 21.7 mm Hg; diastolic: 17.8 mm Hg; nighttime—systolic: 16.9 mm Hg; diastolic: 15.3 mm Hg), while for the ARV, the values were greater at nighttime than at daytime for both BP (daytime—systolic: 7.8 mm Hg; diastolic: 6.4 mm Hg; nighttime—systolic: 8.1 mm Hg; diastolic: 7.3 mm Hg). Nondipper status was observed most frequently for systolic than diastolic BP. The nocturnal dipping average observed was higher for diastolic than for systolic BP, while sleep-through morning surge average observed was higher for systolic BP, and preawakening morning surge there was almost no difference between systolic and diastolic BP average (Table 1).

Among hypertensive participants, 264 (79.5%) of them used antihypertensives. The classes most used in treatment with one or more drugs were angiotensin II receptor antagonists (18.9%), followed by ACE (15.5%) and beta-blockers (9.4%). Drugs were most commonly used in the morning (56.8%), or the morning and evening (24.2%).

Systolic and diastolic diurnal BP variations were reduced by the choice of the 36 most representative shape points (common number

of measures of participants) by RDPa and were grouped into three clusters each one. The average of systolic and diastolic diurnal BP variations for each cluster is represented in Figure 1. The low cluster represents the lowest diurnal BP variation cluster, medium cluster represents the medium diurnal BP variation cluster, and high cluster represents the highest diurnal BP variation cluster, for both systolic and diastolic diurnal BP variations. High clusters have a significantly higher proportion of hypertensive participants (77.6%—systolic; 73.0%—diastolic), males (61.2%—systolic; 70.0%—diastolic), overweight (51%—systolic) and obese (31%—diastolic), "pardos" (41.8%—systolic), and blacks (16.3%—systolic). The characteristics of the participants for the most frequent combinations of systolic and diastolic diurnal BP variation patterns were analyzed (Table S1).

Table 2 presents the ABPM parameters for each cluster. High cluster presented significantly higher averages and standard deviations for 24 h, daytime, and nighttime periods, for both systolic BP and diastolic BP. There was a significant difference between the clusters regarding the ABPM parameters of systolic BP, which was not observed for the diastolic BP clusters regarding the ARV, BP velocity, and dipper status. The high cluster showed significantly higher values for ARV and BP velocity averages, for systolic BP. The highest ARV averages were observed during nighttime, while for BP velocity and standard deviation, the highest averages occurred in the daytime. Furthermore, the high cluster also had a significantly higher proportion of nondippers participants (44%—systolic) and the lowest average dipping (10%—systolic; 16%—diastolic), while the average morning surge parameters were significantly higher (sleep-through morning surge, 21.8 mm Hg —systolic and 21.4 mm Hg —diastolic; preawakening morning surge, 15.5 mm Hg —diastolic).

The multinomial models were adjusted considering as dependent variable the cluster, and the low cluster was used as reference (Figure 2). Concerning the systolic BP, race/color was a significant variable, and "pardos" had greater odds of being in the high cluster than in low cluster (OR = 1.99, CI $_{95\%}$ [1.17; 3.36]). Hypertension was associated with increased odds to be in the high and in the medium clusters (OR = 1.56, CI $_{95\%}$ [1.12; 2.17] and OR = 7.02, CI $_{95\%}$ [4.06; 12.1], respectively), as well as male sex (OR = 1.95, CI $_{95\%}$ [1.42; 2.67] and OR = 1.69, CI $_{95\%}$ [1.04; 2.77], respectively) and overweight (OR = 1.64, CI $_{95\%}$ [1.13; 2.37] and OR = 1.84, CI $_{95\%}$ [1.001; 3.38], respectively). Obese participants had greater odds to be in medium cluster (OR = 1.65, CI $_{95\%}$ [1.08; 2.51]).

Regarding diastolic BP, hypertensive participants (OR = 1.42, CI $_{95\%}$ [1.01; 1.99] and OR = 4.67, CI $_{95\%}$ [2.78; 7.86]), men (OR = 2.41, CI $_{95\%}$ [1.74; 3.34] and OR = 3.29, CI $_{95\%}$ [1.99; 5.45]), and "pardos" (OR = 1.46, CI $_{95\%}$ [1.02; 2.1] and OR = 1.96, CI $_{95\%}$ [1.16; 3.30]) had greater odds to be in high and medium clusters, respectively. Overweight (OR = 1.86, CI $_{95\%}$ [1.27; 2.71]) and weak physical activity (OR = 1.72, CI $_{95\%}$ [1.01; 2.93]) were associated with greater odds to be in medium cluster. The intercept for medium cluster for both models was <.01 with CI with amplitude <.01.

Table 3 presents the results of the mixed-effect models for all clusters and the estimates for systolic and diastolic BP velocity in each period (work, home, sleep1, sleep2, and morning). Initially, five linear splines were included as fixed effects, indicating the five time periods. An improvement in the model fit was identified when the AR1 structure was used and the splines were added as random effects for both systolic BP and diastolic BP (LTR < .01). The estimates for BP velocity over all five periods of time differed significantly from zero (for all models $p < .001$) for all clusters. Four periods of time presented significantly higher values for BP velocity estimates for both patterns of systolic and diastolic diurnal BP variations: home, sleep1, sleep2, and morning.

The fastest rise and fall of systolic BP patterns occurred during the sleep period for all clusters, and high cluster had the highest BP velocities estimates: −4.98 mm Hg/h (sleep1) and 4.24 mm Hg/h (sleep2) that correspond to the period when the participant goes to sleep until the lowest sleep reading and from lowest reading to the last sleep reading, respectively (Table 3).

The largest variation in BP velocity estimates for low and medium systolic clusters was observed in sleep1 and sleep2 periods (SE = 2.46 and SE = 1.68—low cluster, and SE = 2.51 and SE = 2.01—medium cluster), while for the high cluster, the largest variations in BP velocity estimates were observed in the sleep1 and morning periods (SE = 3.17 and SE = 3.78, respectively). The variation over an individual diurnal BP variation was greater in the high cluster (residual

TABLE 1 ABPM parameters of the study population for systolic and diastolic blood pressure

	Total (n = 782)	
ABPM parameters	**Systolic BP**	**Diastolic BP**
Mean of 24 h, mm Hg	124.7 ± 11.8	78.8 ± 8.8
Mean of daytime, mm Hg	128.6 ± 11.9	82.4 ± 8.9
Mean of nighttime, mm Hg	112.8 ± 12.8	67.9 ± 9.5
SD of 24 h, mm Hg	11.8 ± 2.7	10.1 ± 2.1
SD of daytime, mm Hg	9.4 ± 2.4	7.6 ± 1.9
SD of nighttime, mm Hg	8.7 ± 2.7	7.8 ± 2.4
ARV of 24 h, mm Hg	8.0 ± 1.5	6.8 ± 1.4
ARV of daytime, mm Hg	7.8 ± 1.8	6.4 ± 1.6
ARV of nighttime, mm Hg	8.1 ± 2.6	7.3 ± 2.5
BP velocity of 24 h, mm Hg/h	20.5 ± 3.7	17.4 ± 3.2
BP velocity of daytime, mm Hg/h	21.7 ± 4.9	17.8 ± 4.4
BP velocity of nighttime, mm Hg/h	16.9 ± 5.4	15.3 ± 5.1
Nocturnal dipping	0.12 ± 0.06	0.17 ± 0.07
Nondipper status, n (%)	251 (32.1)	112 (14.3)
Sleep-through morning surge, mm Hg	20.6 ± 9.6	19.2 ± 7.9
Preawakening morning surge, mm Hg	14.5 ± 9.2	14.2 ± 7.2

Abbreviations: ABPM, ambulatory blood pressure monitoring; ARV, average real variability; BP, blood pressure; SD, standard deviation.

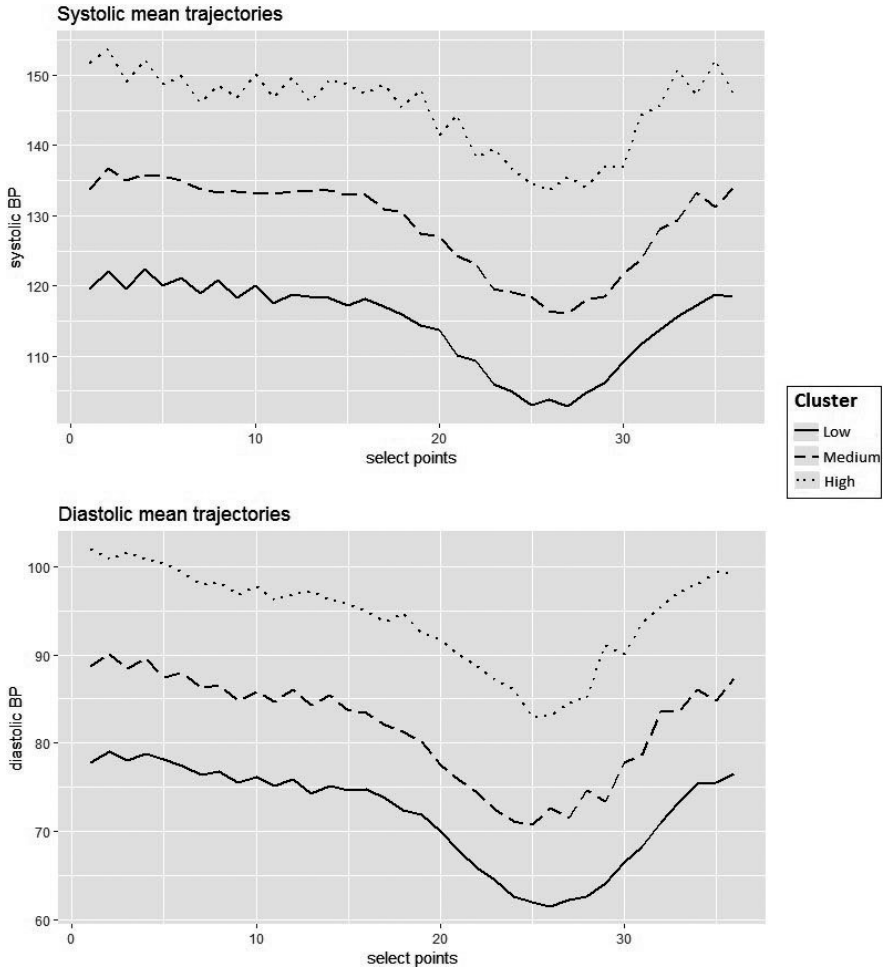

FIGURE 1 Average of systolic and diastolic diurnal BP variation clusters. Low cluster indicates the lowest diurnal BP variation cluster; medium cluster, the medium diurnal BP variation cluster; and high cluster, the highest diurnal BP variation cluster. The 36 selected points were chosen based on the RDPa

SE = 10.46) than in low and medium clusters (residual SE = 8.62 and residual SE = 9.56, respectively).

Similarly to the systolic BP, the diastolic BP patterns present the fastest rise and fall in the sleep period for all clusters and high cluster had the highest BP velocity estimates: −4.99 mm Hg/h (sleep1) and 5.09 mm Hg/h (sleep2) (Table 3). The largest variation in BP velocity estimates for the low cluster was observed in sleep1 and morning periods (SE = 3.40 and SE = 1.40), while for medium and high clusters, it was observed in sleep1 and sleep2 periods (SE = 4.18 and SE = 1.50—medium cluster, and SE = 4.15 and SE = 2.50—high cluster). The variation over an individual diurnal BP variation was greater in the high cluster (residual SE = 8.18) than in low and medium clusters (residual SE = 7.58 and residual SE = 7.57, respectively).

4 | DISCUSSION

Identifying and characterizing daily BP patterns is still an open question in the literature. Our study has shown that it is possible to identify patterns of diurnal BP variation and suggests that higher diurnal BP variation has the worst profile concerning ABPM parameters associated with cardiovascular risk. Moreover, four moments of the day with higher BP variability emerged as important markers of variability in all daily BP patterns: home fall, sleep fall, sleep rise, and morning rise.

The relationship between clinical and behavioral factors and ABPM parameters is well documented in the literature,[10,11,19,20] but the effect of individual factors on diurnal BP variation is still unknown. In our study, we showed that sex, race/color, hypertension, BMI, and physical activity are factors associated with daily BP patterns.

Similarities can be observed between the dynamics of fall and rise of systolic and diastolic daily BP patterns (Figure 1), which was expected given that both BP usually follow the proximal tendencies.[8] Furthermore, similarities were also found with regard to the ABPM parameters and covariables associated with daily BP patterns. High cluster presented the highest systolic and diastolic BP averages and standard deviations during 24-h, daytime, and nighttime periods, and the dipping averages were significantly lower, while the morning surge parameters were higher. Differences between systolic and

TABLE 2 ABPM parameters for systolic and diastolic diurnal BP variation clusters

	Total (*n* = 782)							
	Systolic BP				Diastolic BP			
ABPM parameters	Low *n* = 348	Medium *n* = 336	High *n* = 98	*p*	Low *n* = 362	Medium *n* = 320	High *n* = 100	*p*
Mean of 24 h, mm Hg	114.8 ± 5.4	128.9 ± 5.4	145.2 ± 8.6	<.001	71.9 ± 5.1	81.8 ± 3.9	94.1 ± 5.4	<.001
Mean of daytime, mm Hg	118.6 ± 5.9	133.0 ± 5.9	148.6 ± 8.6	<.001	75.5 ± 5.4	85.5 ± 4.2	97.5 ± 5.64	<.001
Mean of nighttime, mm Hg	103.6 ± 7.0	116.3 ± 7.7	133.7 ± 12.4	<.001	61.5 ± 6.0	70.7 ± 5.9	82.1 ± 8.3	<.001
SD of 24 h, mm Hg	11.1 ± 2.5	12.2 ± 2.6	12.9 ± 3.3	<.001	9.9 ± 1.9	10.2 ± 2.2	10.9 ± 2.4	<.001
SD of daytime, mm Hg	8.7 ± 2.1	9.7 ± 2.2	10.8 ± 3.0	<.001	7.5 ± 1.8	7.5 ± 1.8	8.3 ± 2.4	.003
SD of nighttime, mm Hg	8.2 ± 2.3	8.9 ± 2.7	9.5 ± 3.3	<.001	7.5 ± 2.2	7.9 ± 2.3	8.2 ± 2.9	.003
ARV of 24 h, mm Hg	7.6 ± 1.4	8.2 ± 1.5	8.9 ± 1.6	<.001	6.8 ± 1.4	6.7 ± 1.2	7.0 ± 1.6	.52
Arv of daytime, mm Hg	7.4 ± 1.7	8.0 ± 1.8	8.5 ± 1.9	<.001	6.5 ± 1.7	6.3 ± 1.5	6.4 ± 1.7	.35
Arv of nighttime, mm Hg	7.8 ± 2.4	8.4 ± 2.7	8.7 ± 2.7	<.001	7.2 ± 2.5	7.4 ± 2.4	7.6 ± 2.8	.15
BP velocity of 24 h, mm Hg/h	19.4 ± 3.4	20.9 ± 3.6	22.4 ± 3.7	<.001	17.3 ± 3.4	17.2 ± 2.9	17.9 ± 3.5	.14
BP velocity of daytime, mm Hg/h	20.5 ± 4.5	22.3 ± 4.9	23.7 ± 4.8	<.001	17.8 ± 4.6	17.7 ± 4.2	18.1 ± 4.3	.82
BP velocity of nighttime, mm Hg/h	16.2 ± 5.0	17.6 ± 5.6	17.8 ± 5.6	<.001	15.1 ± 5.2	15.4 ± 5.0	15.6 ± 5.6	0.40
Nocturnal dipping	0.13 ± 0.05	0.12 ± 0.05	0.10 ± 0.07	.001	0.18 ± 0.07	0.17 ± 0.07	0.16 ± 0.08	<.001
Nondipper status, *n* (%)	102 (29)	106 (31)	43 (44)	.02	43 (12)	51 (16)	18 (18)	0.17
Sleep-through morning surge, mm Hg	19.1 ± 8.5	21.8 ± 9.6	21.8 ± 11.9	.001	18.1 ± 7.4	19.7 ± 7.5	21.4 ± 9.6	<.001
Preawakening morning surge, mm Hg	13.6 ± 8.2	15.5 ± 9.2	14.6 ± 11.5	.05	13.4 ± 7.0	14.7 ± 6.4	15.5 ± 9.2	.003

Abbreviations: ABPM, ambulatory blood pressure monitoring; ARV, average real variability; BP, blood pressure; SD, standard deviation.

diastolic daily BP patterns were found for ARV, BP velocity, and the percentage of nondippers that were significantly different only between the clusters of systolic diurnal BP variation. Differences between systolic and diastolic BP variability were expected since in general, the systolic BP presents a greater variability than the diastolic over the daily activities.[36]

Multinomial models showed that hypertensive and men had a greater odd of being in high and medium clusters. "Pardos" had a greater odd of being in the high cluster and overweight in the medium cluster for both systolic and diastolic daily BP patterns. The fact that hypertensive and men have higher odds of being in the high cluster, cluster with higher BP average, higher systolic BP variability, lower dipping, and higher morning surge parameters is consistent with results reported in the literature that indicate that hypertensive, in general, have higher BP variability and lower dipping[16,18] and BP is higher in men than in women at similar ages, as well as morning surge.[37,38] For race/color, it is known that ABPM shows that blacks have a greater BP average and variability and blunted dipping than whites.[5,10,19,20] Particularly in Brazil, studies have already explained differences in the prevalence of hypertension among "pardos" and blacks[39,40] but there is still lack of studies on the impact of the race/color on the ABPM parameters.

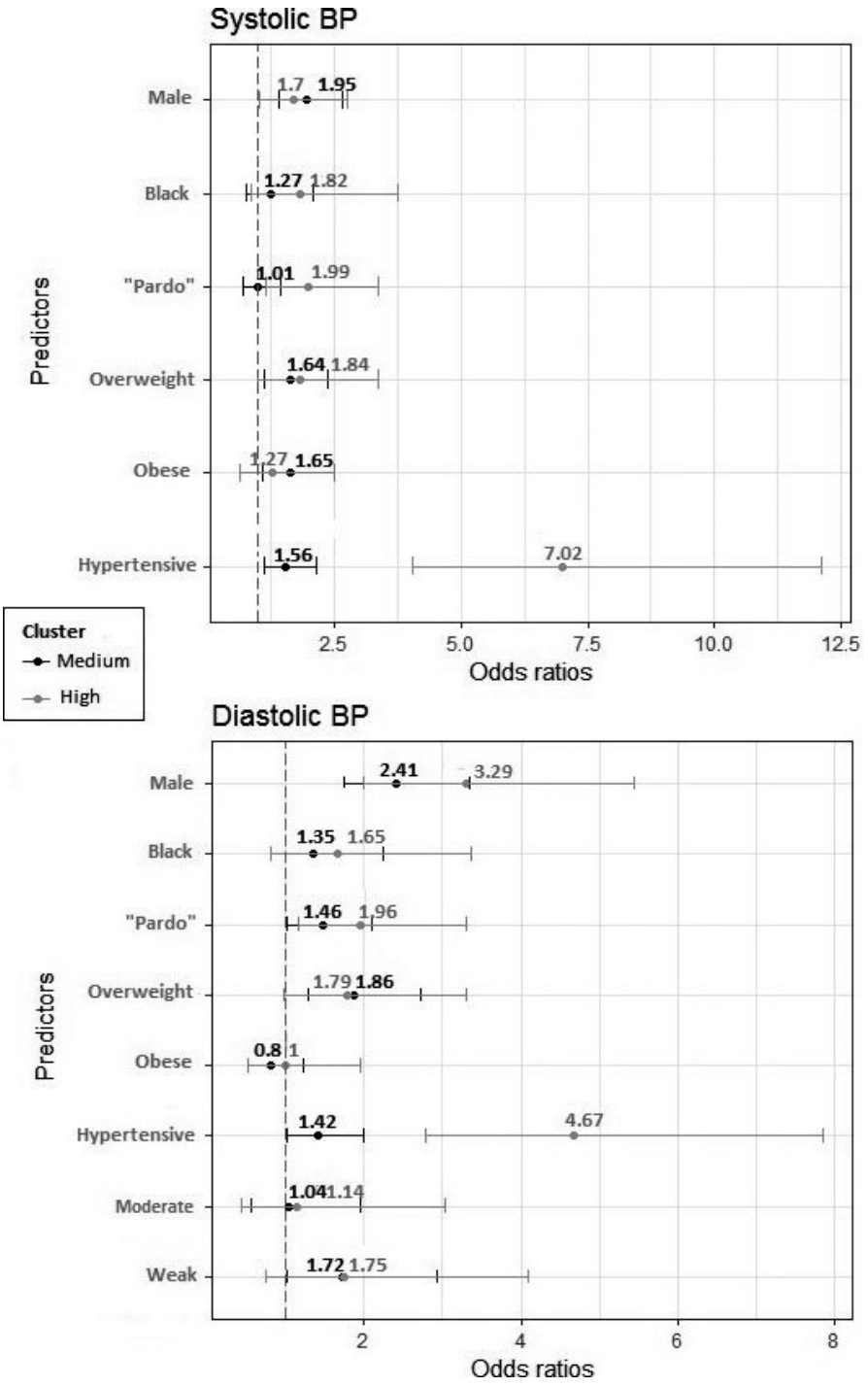

FIGURE 2 Odds ratios for the multinomial models adjusted for the systolic and diastolic diurnal BP variation clusters. For the systolic diurnal BP variation clusters, the significant covariables were sex, race/color, BMI, and hypertension. For the diastolic diurnal BP variation clusters, the significant covariables were sex, race/color, BMI, hypertension, and physical activity

The results of the mixed-effect models confirmed the similarities in the variability dynamics observed in Figure 1 for systolic and diastolic clusters. The daily BP patterns are sequences of faster and faster falls at work, at home, and during sleep1 (sleep fall), followed by the fastest BP rise over the day (sleep2—sleep rise) and morning rise. The analysis of BP variability in the five periods of the day showed four markers of greatest BP variability in all clusters: home, sleep1, sleep2, and morning. In general, the higher is the level of the diurnal BP variation, the higher are the estimates for BP variability in each of the five periods analyzed which is consistent with some studies.[20,41] The exception was the high cluster, which for systolic diurnal BP variation showed lower variability than the other clusters in the home and morning periods. For diastolic diurnal BP variation, the estimate for BP variability in the high cluster in the morning was

TABLE 3 Results of BP variability estimates over the day and 95% CI from the mixed-effects models for systolic and diastolic diurnal BP variation clusters

	Systolic BP			Diastolic BP		
	Low cluster	Medium cluster	High cluster	Low cluster	Medium cluster	High cluster
BP at first, mm Hg	119 (117.8; 120.3)*	133.1 (131.4; 134.8)*	148.5 (142.1; 154.8)*	78.1 (75.8; 80.4)*	87.9 (85.8; 90.1)*	97.5 (90.9; 104.9)*
Time Period						
Work, mm Hg/h	−0.24 (−0.35; −0.13)*	−0.26 (−0.39; −0.14)*	−0.31 (−0.61; −0.006)*	−0.4 (−0.48; −0.32)*	−0.48 (−0.57; −0.39)*	−0.56 (−0.78; −0.33)*
Home, mm Hg/h	−1.3 (−1.47; −1.12)*	−1.62 (−1.83; −1.4)*	−1.28 (−1.76; −0.79)*	−1.33 (−1.47; −1.18)*	−1.46 (−1.64; −1.27)*	−1.59 (−1.94; −1.24)*
Sleep1, mm Hg/h	−4.37 (−4.71; −4.02)*	−4.52 (−4.89; −4.15)*	−4.98 (−5.82; −4.14)*	−4.62 (−5.05; −4.20)*	−5.54 (−6.08; −5.0)*	−4.99 (−5.96; −4.03)*
Sleep2, mm Hg/h	3.6 (3.29; 3.91)*	4.11 (3.74; 4.48)*	4.24 (3.52; 4.97)*	3.18 (2.94; 3.41)*	3.6 (3.34; 3.87)*	5.09 (4.38; 5.8)*
Morning, mm Hg/h	3.18 (2.88; 3.48)*	3.66 (3.3; 4.01)*	2.97 (2.03; 3.91)*	2.87 (2.62; 3.12)*	2.93 (2.67; 3.19)*	2.55 (1.99; 3.11)*

Note: Model: fixed effects (linear splines), random effects (linear splines).
*p-value <.05.

also lower than in the other clusters and the BP variability in the sleep1 period was lower than in medium cluster. However, the main difference found was that the diastolic BP rise in the sleep period was faster than the fall. This differentiated behavior indicates a possible risk profile for this daily BP pattern since the elevation in sleep before awakening is related to many cardiovascular events in the morning.[42]

It is possible that the differentiated behavior for the high cluster for systolic and diastolic diurnal BP variations, particularly in the morning and evening, is related to the fact that it is the cluster with the highest percentage of hypertensive participants and the times when the antihypertensive drugs are administered could affect the BP values and variability.[43] Not only antihypertensives but other classes of drugs such as anxiolytics, psychoactive, and associations could affect variability.[44]

In our study, it is not possible to analyze the effect of the pharmacological classes of antihypertensives and its combinations in the ABPM parameters and variability, due to the frequency of participants in each therapeutic scheme. However, it is important to note that the homogeneity of the diurnal BP variation within each cluster implies similar ABPM parameters for the individuals grouped, regardless of antihypertensive use (Table S2). The difference between therapeutic schemes would help us to understand the differences between daily BP patterns. In addition to drugs, factors such as sleep quality and stress can influence BP parameters and should be considered when analyzing diurnal BP patterns and variability.[45,46] Other ABPM studies are necessary to evaluate the effect of these factors on daily BP patterns.

It is important to stress that our study characterizes the diurnal BP variation patterns for systolic and diastolic BP separately. Due to the relationship between systolic and diastolic BP readings throughout the day, the ABPM parameters, variability estimates, and profiles associated with the patterns may change when combined patterns of systolic and diastolic BP are analyzed.

Our study is the first study we have reported to identify and characterize daily BP patterns. The ABPM parameters do not allow a complete characterization of the BP behavior throughout the 24 h of the day. The parameters belong to the context of the diurnal BP variation and are related to each other, bringing this context together with the parameters can provide the correct assessment of cardiovascular risk.

The findings of the current study showed similarities between systolic and diastolic daily BP patterns. Clusters with higher diurnal BP variation have the worst profile concerning ABPM parameters related to cardiovascular risk and, in the sleep period, greater systolic variability and rise faster than fall on diastolic BP. Hypertensive, "pardos," and men had greater odds of having these diurnal BP variation patterns.

The daily patterns and markers of variability identified in this study contribute to the characterization of diurnal BP variation. The identification and characterization of daily BP patterns is still an open problem in the literature that dialogues with the inexistence of consolidated thresholds for the parameters of morning surge and BP variability and makes it unfeasible to use in clinical practice. The integrated study of ABPM parameters through daily BP patterns can help in the assessment of risk for cardiovascular events.

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CONFLICT OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

AUTHOR CONTRIBUTION

Daniela Paula participated in the conception, analysis, interpretation of data, and drafting of the work. Leidjaira Lopes participated in the acquisition, interpretation of data, and revising the work critically. Jose Mill participated in interpretation of data, revising the work critically, and final approval. Maria Fonseca participated in the acquisition, interpretation of data, revising the manuscript critically, and final approval. Rosane Griep participated in the acquisition, interpretation of data, revising the manuscript critically, and final approval. Each author accepted accountability for all aspects of the work by ensuring that questions on the accuracy or integrity of any part of the work were appropriately investigated and resolved.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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