Dipping Is Superior to Cusums Analysis in Assessment of the Risk of Stroke in a Case-Control Study

Robert A. Phillips, Alexander Butkevich, Kara F. Sheinart, and Stanley Tuhrim

Background: Blunted nocturnal decline in blood pressure (BP) is associated with increased risk of stroke. Mean day–night BP difference (dipping) and cusums-derived circadian alteration magnitude (CDCAM) of BP are the common measures of diurnal BP variation. Although a significant number of clinical trials have demonstrated that dipping is associated with a lower risk of cardiovascular events, the clinical value of CDCAM of BP is unknown. We evaluated the association between dipping and CDCAM of BP and the risk of stroke.

Methods: We analyzed 24-h ambulatory BP recordings of 110 control subjects and 91 stroke survivors enrolled in a case-control stroke study. Nondipping was defined as nocturnal drop of $<$ 10 mm Hg in systolic BP. The associations between nondipping, CDCAM of BP, and risk of stroke were calculated in the same sample.

Results: There were significantly fewer nondippers in the control group as compared with those among the stroke survivors. The odds ratio for stroke of nondippers was 2.3. By contrast, there was no significant difference in CDCAM of systolic BP between the control and stroke survivor groups. This finding could not be explained by the presence of reverse dippers in both groups.

Conclusions: In this case-control study, classification of subjects into dippers and nondippers was found to be more clinically useful than cusums analysis of BP profile. Analysis of prospective data is needed to determine the clinical value of the cusums analysis of BP profile. Am J Hypertens 2001;14:649–652 © 2001 American Journal of Hypertension, Ltd.

Key Words: Ambulatory blood pressure monitoring, cusums, dipping, stroke.

Twenty-four-hour ambulatory blood pressure monitoring (ABPM) is becoming a widely used procedure for evaluation of subjects with suspected and diagnosed hypertension.[1] The 24-h blood pressure (BP) of most individuals exhibits a characteristic nocturnal decline relative to daytime values, which is referred to as dipping.[2,3] Several methods are used for evaluation of a subject's BP profile; the most common are the classification into dippers and nondippers based on the mean BP during predefined day and night intervals and on cumulative sums (cusums) analysis.

Classification into dippers and nondippers is based on the difference between a subject's mean daytime and nighttime BP. Daytime and nighttime can be defined in a variety of ways: for example, according to fixed clock times, a subject's reported sleep and waking times, or wrist actigraphy.[4,5] Likewise, there are various definitions of dipping used in several clinical studies.[2,6–10] These varied definitions result in different classifications of dipper status.[11] To the best of our knowledge, there are no data, nor is there a consensus, regarding what definition is clinically the most valid.

Cusums analysis of BP profile[12,13] does not involve definitions of daytime and nighttime. With this technique, one calculates the minimal and maximal sustained BP during certain time periods (usually 6 h). The difference between the minimal and maximal BP is referred to as cusums-derived circadian alteration magnitude (CDCAM) of BP. Being independent of the definitions of daytime and nighttime, CDCAM of BP is more reproducible than are day–night differences.[13–15] However, although a significant number of clinical trials have demonstrated that nocturnal decline in systolic BP is associated with a lower risk of hypertensive target organ damage, cardiovascular events, and mortality,[10,16–19] data on the relationship between cardiovascular risk and CDCAM of BP are lacking.

The aim of our study was to compare the association of

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From the Hypertension Section (RAP, AB), Zena and Michael A. Wiener Cardiovascular Institute, USA and Department of Neurology (KFS, ST), Mount Sinai Medical Center, New York, New York.

Address correspondence and reprint requests to Alexander Butkevich, MD, MSc, and Robert A. Phillips, MD, PhD, FACC, Box 1085, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029; e-mail: robert.phillips@mssm.edu

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dipping and CDCAM of systolic and diastolic BP with the risk of stroke in a case-control, stroke-related study.

Methods

Subjects and ABPM Recordings

The study population consisted of 110 control subjects and 91 stroke survivors enrolled in the Minority Risk Factors and Stroke Study (MRFASS), all of whom underwent 24-h ambulatory BP monitoring (ABPM). The patient selection criteria and baseline characteristics are described in detail elsewhere.[20,21] Briefly, patients were eligible for participation in the study if they were ≥ 45 years of age and were admitted into one of the study hospitals with an ischemic stroke or intracerebral hemorrhage of < 5 days duration between November 1, 1991 and May 1, 1995. Control subjects were recruited among the residents of the hospitals' catchment area; they were ≥ 45 years of age and did not have a history of stroke. All patients and control subjects who were enrolled in the MRFASS study, who agreed to have ABPM performed, and who had at least one valid BP measurement in every 1-h period, were included in this study. Ambulatory BP monitoring was performed with SpaceLabs 90207 or 90217 monitor (SpaceLabs Medical, Redmond, WA). In stroke survivors, ABPM was performed ≥ 1 week poststroke. The monitors were programmed to measure BP every 20 min during the subjects' reported waking hours, and every 30 min during sleeping hours. The subjects were instructed to engage in their usual activities during the day of ABPM.

The study was approved by the institutional review board of the Mount Sinai Medical Center. Written informed consent was obtained from all subjects before enrollment in the study.

ABPM Analyses

Twenty-four-hour ABPM recordings were downloaded from the monitors into the 90121 ABP Report Management System, version 1.03.02 (SpaceLabs Medical) and then into the MS Access 97 (Microsoft, Redmond, WA) database. The BP recordings were edited by the computer according to the following criteria[22,23]: systolic BP ≥ 70 and ≤ 260 mm Hg, diastolic BP ≥ 40 and ≤ 150 mm Hg, pulse pressure ≥ 20 mm Hg, and heart rate ≥ 20 and ≤ 200 beats/min. Average daytime and nighttime BP were calculated as mean BP between 7 AM and 10 PM for daytime and between 10 PM and 7 AM for nighttime.

Cusums Analysis

Mean BP during the ABPM recording was taken as a reference value. The ABPM record was divided into 1-h periods; mean BP during every period was subtracted from the reference value and the cumulative difference plotted as a function of time, thus yielding a modified cusums plot. The slope of the plot over a specific period represents the difference between the reference BP and the mean BP during this period. Trough and crest BP values were defined as the maximal and minimal slopes of the modified cusums plot during 6-h periods. The CDCAM of systolic and diastolic BP were calculated as differences between crest and trough BP.

The data were analyzed with the use of MS Access 97 and MS Excel 97 (as parts of the MS Office 97; Microsoft) programs. Statistical analyses were performed with the use of the SigmaStat 2.0 (SPSS, Chicago, IL) program. Numerical variables were compared with the *t* test; the z-test was used to compare proportions. A value of $P < .05$ was chosen as the level of statistical significance.

Results

Patient Characteristics

The subjects' age and body mass index did not differ significantly between the two groups. There were significantly fewer women and more African Americans among stroke survivors. As expected, both daytime and nighttime BP (with the exception of daytime diastolic BP) were significantly higher in the stroke survivors group, as was the proportion of hypertensive subjects. Stroke survivors were more likely to be diabetic or to receive vasoactive medications. In all, 72% of the stroke survivors were mobile (ie, walking). The subjects' characteristics are summarized in Table 1.

Nondipping and Risk of Stroke

There were significantly fewer dippers in the stroke survivors group than in the control group (Table 2). The unadjusted odds ratio (OR) for stroke of nondippers was 2.3 (95% confidence interval 1.4 to 4.0). The definition of dipping (nocturnal decline in systolic BP of 10 mm Hg or 10%, nocturnal decline of 10 mm Hg in systolic BP and of 5 mm Hg in diastolic BP, or nocturnal decline of 10% in both systolic and diastolic BP) did not alter the OR significantly. In the multiple regression analysis adjusting for sex and blood pressure, the odds ratio of nondippers for stroke was 2.3 (95% confidence interval 1.3 to 3.8, $P = .011$)

CDCAM of BP in Control Subjects and Stroke Survivors

The CDCAM of both systolic and diastolic BP was slightly blunted in stroke survivors as compared with that in the control subjects (Table 3). However, unlike the proportions of nondippers, the difference in CDCAM of systolic BP did not reach statistical significance. There was a 3 mm Hg difference in CDCAM of diastolic BP between the stroke survivors and control subjects. This difference was statistically significant.

The CDCAM of BP is a measure of the absolute change in BP during a 24-h period. Thus, a subject's CDCAM of BP may be similar if that subject exhibits a nocturnal rise of BP (reverse dipping) or a decline in BP. Reverse dip-

Table 1. Patient Characteristics

	Controls	Stroke Survivors	*P*
Age (y)	68.1 ± 9.1	68.6 ± 11.3	.728
Women (%)	72	49	.001
African Americans (%)	30	45	.040
Whites (%)	49	35	.063
Hispanics (%)	21	23	.864
BMI (kg/m^2)	26.2 ± 4.6	27.4 ± 5.1	.081
Blood pressure (mm Hg)			
Daytime	133 ± 17/78 ± 8	144 ± 22/80 ± 11	<.001/.137
Nighttime	122 ± 20/69 ± 9	138 ± 24/75 ± 12	<.001/<.001
Hypertensives (%)	44	65	.005
On vasoactive medications (%)	46	63	.023
Diabetic (%)	9	24	.007

Data are mean ± SD. Hypertensive subjects were defined as those with daytime BP≥135/85 mm Hg.

pers, however, as compared with dippers and nondippers, are at an increased risk of cardiovascular events.[16] To evaluate whether reverse dipping may account for the lack of difference in CDCAM of BP between the two groups, we compared the CDCAM of systolic and diastolic BP in the two groups, when the reverse dippers (defined as subjects with a nocturnal rise of 10 mm Hg in systolic BP) were omitted. Elimination of reverse dippers from the analysis did not significantly affect the results (Table 3).

Discussion

The aim of this study was to compare, in a case-control study, the association between nondipping, CDCAM of BP, and relative risk of stroke. In keeping with previous findings, nondipping was associated with a higher risk of stroke.[10,21] Changing the criteria for dipping did not significantly affect the nondipping odds ratio for stroke.

Although there were significantly fewer dippers in the stroke survivor group than in the control group, CDCAM of systolic BP was not significantly different between the groups. Although the difference in CDCAM of diastolic BP did reach the level of statistical significance, a large prospective PIUMA study[19] showed that nocturnal decline in diastolic BP was not associated with a lower risk of cardiovascular events. Thus, despite the statistical significance of the study findings, the clinical significance of CDCAM of diastolic BP may be doubtful.

Being independent of time, CDCAM of BP is more reproducible than day–night BP difference. However, it was not useful as a risk marker of stroke in our study. Several explanations of this apparent discrepancy are possible. One is that CDCAM of BP is a measure of an absolute variation of BP, regardless of BP profile. Thus, reverse dippers (that is, those individuals with a nocturnal increase in BP) may have a CDCAM of BP similar to that of dippers. A larger number of reverse dippers in the stroke survivor group could theoretically account for the similar CDCAM of BP in both groups. This possibility is unlikely, however, as the results did not change significantly when we excluded reverse dippers from the analysis. A more likely possibility is that it is the decrease in BP during the night (or sleep period) that is physiologically important. If this were the case, then nondipping at night would be associated with higher cardiovascular risk even in the presence of significant CDCAM of BP, which may be reflecting BP changes during the day.

Table 2. Proportions of nondippers as determined by different definitions in control subjects and stroke survivors

	Controls	Stroke Survivors	*P*
Nondippers (10 mm Hg)	46%	66%	.007
Nondippers (10%)	59%	77%	.011
Nondippers (10/5 mm Hg)	46%	69%	.002
Nondippers (10/10%)	64%	79%	.030

Table 3. CDCAM (mean ± SD) of systolic and diastolic BP in control subjects and stroke survivors

CDCAM	Controls	Stroke Survivors	*P*
With reverse dippers			
CDCAM of SBP	25 ± 9	24 ± 10	.151
CDCAM of DBP	18 ± 6	15 ± 6	.01
Without reverse dippers			
CDCAM of SBP	24 ± 9	24 ± 10	.157
CDCAM of DBP	18 ± 6	16 ± 6	.01

CDCAM = cusums-derived circadian alteration magnitude; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Using cusums analysis, Dawson et al[24] showed a blunted nocturnal BP change in stroke survivors within 48 h of the event. Inasmuch as ABPM was not performed in the acute phase of stroke in our study, this may account for the fact that we did not find a significant difference in CDCAM of systolic and diastolic BP between the control subjects and stroke survivors. We propose that blunted circadian variation of BP (at least in the case of systolic BP) is likely to be a transient finding associated with an acute phase of stroke, whereas lack of nocturnal decline in BP is likely to be a risk factor for stroke.

In conclusion, in this case-control study, we found that nondipping was associated with a greater risk of stroke, whereas cusums analysis of 24-h BP profiles was less useful for assessment of the relative risk of stroke. It should be noted, however, that our study may be limited because of its retrospective case-control design. Analysis of prospective data would further clarify the clinical usefulness of the cusums analysis of 24-h BP profiles.

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