Cumulative Sums in Quantifying Circadian Blood Pressure Patterns

Alice Stanton, John Cox, Neil Atkins, Kevin O'Malley, and Eoin O'Brien

The plotting of cumulative sums (cusums), a technique of proven value in the detection of trends in data collected at intervals of time, may be modified to analyze circadian blood pressure patterns quantitatively. Mean 24-hour ambulatory blood pressure is taken as the reference value and is subtracted from each pressure value. The products of the remainders and the corresponding time intervals are summed in sequence and are plotted against time to form a modified cusum plot. The slope of the plot over any given time period equals the difference between mean blood pressure during that period and mean 24-hour blood pressure. Crest and trough blood pressures (the mean blood pressures of the 6-hour periods of highest and lowest pressures) may be identified as the 6-hour periods where plot slopes are most steeply ascending and descending, respectively. The magnitude of the circadian blood pressure change, defined as the difference between crest and trough blood pressure, is calculated from the difference between crest and trough plot slopes. The height of the cusum plot, which reflects pressure alteration extent and duration, may also be used as a measure of circadian pattern. The modified cusums technique and cusum-derived statistics are illustrated using ambulatory blood pressure profiles of hypothetical and actual hypertensive subjects. Independence from fixed time periods improves precision and reproducibility. Cusum-derived statistics are simply calculated from raw ambulatory data and should prove useful in the quantitative analysis of circadian blood pressure profiles. (*Hypertension* 1992;19:93–101)

Blood pressure follows a circadian rhythm.[1,2] Pressure levels are usually lowest during the night, but there is considerable interindividual variability in the extent and duration of the nocturnal blood pressure decline or "dip." Circadian blood pressure patterns tend to be reproducible,[3–5] and deviations from the usual diurnal rhythm may have pathological relevance.[6–12] There is no universally accepted method of quantifying circadian pattern. Calculation of the pressure difference[6,10] or the percent pressure difference[7,13] between average daytime and nighttime blood pressures assumes fixed sleep/wake timings. Halberg's "cosinor method"[14,15] and other statistical analyses, such as separate linear models fitted to the data of each subject[16] or periodic spline models,[17] are complex necessitating remodeling of original data and thus are more suited to qualitative rather than quantitative analyses.

The cumulative sums (cusums) technique is among the simplest statistical methods available.[18,19] It makes possible rapid and powerful assessments of changes in means or in the slopes of trends from data collected at intervals of time. In this technique, an arbitrary but relevant line is drawn across a plot of the data. Successive deviations of the data from that line are then summed and plotted. Sustained higher or lower values than the reference line produce positively and negatively sloping lines, respectively. The magnitude of the slope of the line depends on the difference of the values from the reference value. Changes in the cusum reveal changes in the trend of data from the baseline much more sensitively than do the data themselves. The use of cusums in ambulatory blood pressure data has previously been confined to merely detecting the precise points of change of successive measurements.[20] However, taking mean 24-hour blood pressure as the reference value and multiplying pressure deviations by time permits the adaptation of cusums to quantify nocturnal dipping with independence from fixed time periods.

In this study, we used both hypothetical blood pressure profiles and repeated 24-hour ambulatory blood pressure measurements from a group of 22 hypertensive subjects to illustrate this modification of cusums methodology and also to assess its precision in the characterization of circadian blood pressure patterns.

Methods

Hypothetical Blood Pressure Profiles

A number of blood pressure profiles were generated to allow exploration of the applicability of cusums techniques to the detection and quantification of circadian patterns.

Subjects and Blood Pressure Recording

Twenty-two Caucasian patients with sitting diastolic blood pressures between 90 and 115 mm Hg were selected for this study. Mean age was 53 years (range, 33–67 years). Eleven patients were male. Patients were either previously untreated or had discontinued antihypertensive treatment at least 4 weeks before the study. All gave informed consent to the investigation, which was approved by the Hospital Ethics Committee. Each patient had casual blood pressure measurement and 24-hour automated ambulatory blood pressure monitoring on two occasions separated by a period of 4 weeks. Casual blood pressure was measured according to British Hypertension Society recommendations[21] with a standard mercury sphygmomanometer after the subject had been in the sitting position for 3 minutes. The mean of three readings on each occasion was taken as the casual blood pressure. Twenty-four–hour ambulatory blood pressure was recorded with the SpaceLabs 90202 system (SpaceLabs Inc., Redmond, Wash.).[22] The recorders were programmed to obtain measurements at intervals of 30 minutes for a 24-hour period starting between 9 and 11 AM. Failed recordings automatically triggered a single remeasurement attempt 2 minutes later. If blood pressure recordings were repeatedly unsuccessful, resulting in an interval (time period between two successive ambulatory blood pressure recordings) duration of 2 hours or more, the ambulatory study was regarded as inadequate and was repeated. The devices were programmed to deflate in 4 mm Hg bleed steps.

Construction of Cumulative Sum Plots

Interval blood pressure. Each interval blood pressure is taken as the mean of the blood pressure readings at the start and finish of the interval. Mean 24-hour blood pressure (see "Appendix"), the reference value for construction of the plot, is calculated from these interval pressures, weighted by the duration of the interval; intended interval duration was 30 minutes but varied where there were failed blood pressure recordings. Similarly, mean pressures of all other periods are calculated from interval pressures weighted for time. To construct the cusum plot, mean 24-hour pressure is subtracted from each interval pressure value in succession; any remainder (mm Hg) is multiplied by the duration of the interval (hr) and then the resultant pressure–time product (mm Hg · hr) is added to the previous sum. This cusum, plotted against time, is the cusum plot. When the interval pressure is greater than mean 24-hour blood pressure, the pressure–time product is positive, the cusum increases, and
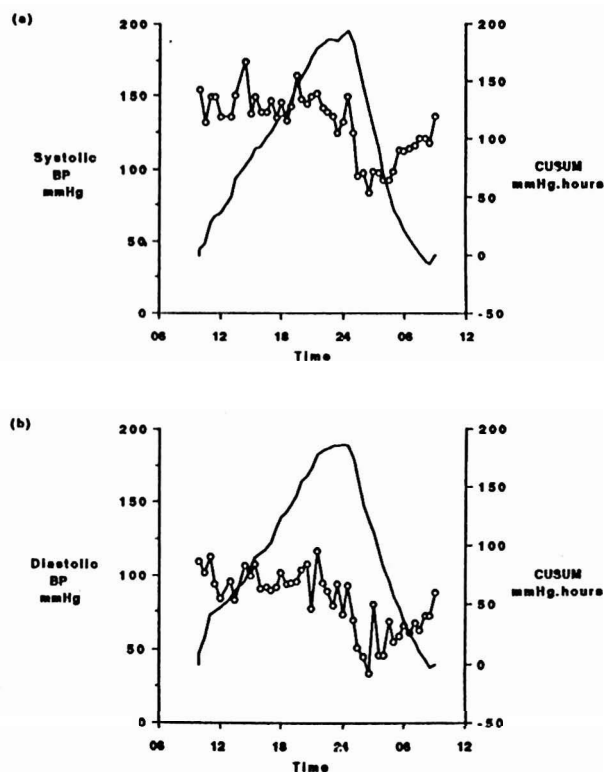

FIGURE 1. Panel a: *Twenty-four–hour ambulatory systolic blood pressure (BP) profile* (○) *from a hypertensive subject with an accentuated nocturnal decline in blood pressure with corresponding cumulative sums (cusum) plot* (−). *Cusum plot height (CPH), 200.5 mm Hg · hr; cusum-derived circadian alteration magnitude (CDCAM), 45.2 mm Hg.* Panel b: *Diastolic blood pressure profile* (○) *from the same subject, with corresponding cusum plot* (−). *CPH, 187.2 mm Hg · hr; CDCAM, 39.1 mm Hg.*

the plot rises. When the interval pressure is less than the reference value, the cusum decreases, and the plot falls. The cusum plot slope (CPS) (see "Appendix") for any given time period is defined as the change in the cusum over a given period of time divided by the change in time for that period. (A period must be composed of whole numbers of intervals.) It equals the difference between the mean time-weighted blood pressure for that period and mean 24-hour blood pressure. The plotting of the cusum of the products of pressure deviations and the corresponding time intervals rather than merely the cusum of pressure deviations is of critical importance to this mathematical relation. Multiplying the pressure deviations by time corrects for missing readings and varying interval duration.

Figure 1A illustrates the systolic pressure profile and Figure 1B the diastolic pressure profile of a hypertensive patient with a pronounced nocturnal dip. In each figure the corresponding systolic and diastolic cusum plots are also illustrated. During daytime hours, blood pressure is much greater than mean 24-hour blood pressure, and thus, both cusum plots show a sharply rising trend. Evening (8 PM to
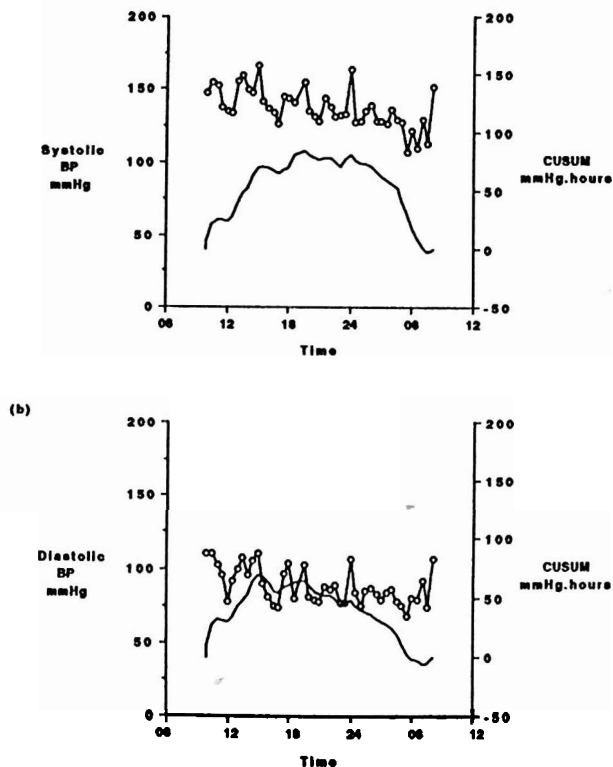
FIGURE 2. Panel a: *Twenty-four–hour ambulatory systolic blood pressure (BP) profile* (○) *from a subject illustrating a flattened circadian rhythm. Corresponding cumulative sums (cusum) plot* (−) *is also shown. Cusum plot height (CPH), 86.2 mm Hg · hr; cusum-derived circadian alteration magnitude (CDCAM), 23.4 mm Hg.* Panel b: *Diastolic BP profile* (○) *and cusum plot* (−) *from the same subject. CPH, 71.4 mm Hg · hr; CDCAM, 18.2 mm Hg.*

FIGURE 3. Panel a: *Twenty-four–hour ambulatory systolic blood pressure (BP) profile* (○) *from a subject whose blood pressure rises nocturnally, with corresponding cumulative sums (cusum) plot* (−). *Cusum plot height (CPH), 94.7 mm Hg · hr; cusum-derived circadian alteration magnitude (CDCAM), 18.6 mm Hg.* Panel b: *Diastolic BP profile* (○) *and cusum plot* (−) *from the same subject. CPH, 60.7 mm Hg · hr; CDCAM, 12.1 mm Hg.*

midnight) blood pressure, although greater than mean 24-hour blood pressure, is lower than daytime blood pressure, and thus the slopes of the plots become less steep in their ascent. At night both systolic and diastolic pressures fall below the mean for the 24-hour period, and the plots show a falling trend until blood pressure rises again the next morning. Figures 2 and 3 show blood pressure profiles from subjects with less pronounced circadian alterations with their corresponding flatter cusum plots. The data in **Figures 3** and **4** differ from those of Figures 1 and 2 in that blood pressure is highest nocturnally and lower during daytime hours.

Calculation of Cumulative Sum–Derived Statistics

Cusum-derived crest blood pressure measures the highest sustained pressures occurring during the 24 hours of monitoring. It is defined as the time-weighted mean blood pressure of the period of at least 6 hours with the highest time-weighted mean pressure level. Six hours was empirically chosen as an appropriate time period to illustrate sustained rather than transient changes in blood pressure. To facilitate computation, time periods had to be composed of whole intervals. To overcome the difficulties raised
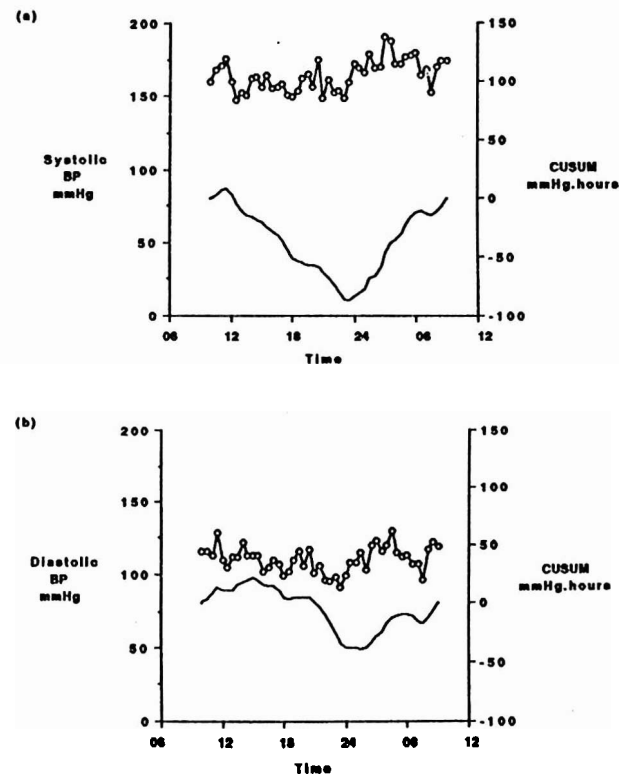
by occasional missed readings and unequal interval durations, it was stipulated that the time periods over which sustained pressure changes were quantified had to be 6 hours or greater. Since CPS over a given time period equals the difference between the mean blood pressure for that period and mean 24-hour blood pressure, cusum-derived crest blood pressure can be located in time from the cusum plot as the 6-hour (or longer) period with the steepest positive slope (crest CPS). It may be calculated as

cusum-derived crest BP=

crest CPS+mean 24-hour BP

Cusum-derived trough blood pressure is defined as the time-weighted blood pressure of the period of at least 6 hours with the lowest time-weighted mean blood pressure level. It is located in similar fashion from the cusum plot as the 6-hour (or longer) period with the most negative slope (trough CPS) and is calculated as
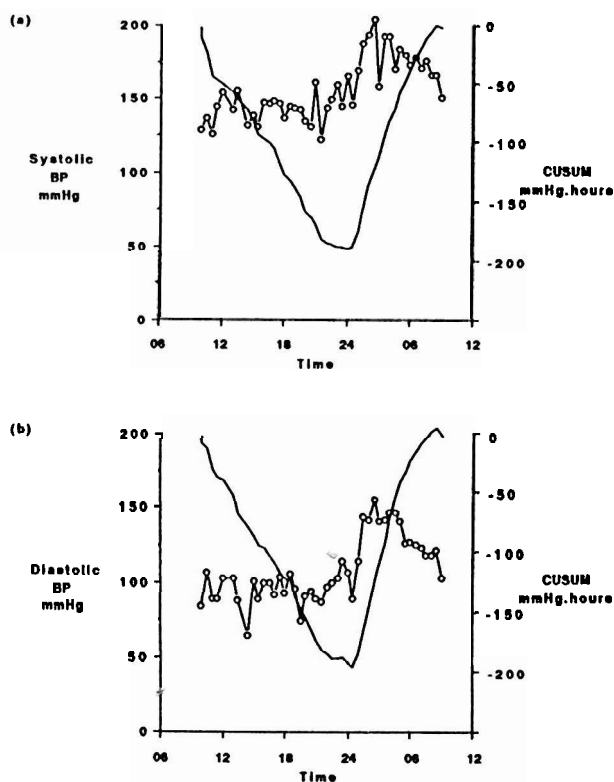
cusum-derived trough BP=

trough CPS+mean 24-hour BP

FIGURE 4. Panel a: *Twenty-four–hour ambulatory systolic blood pressure (BP) profile* (o) *from a subject whose blood pressure rose markedly nocturnally, with corresponding cumulative sums (cusum) plot* (−). *Cusum plot height (CPH), 188.0 mm Hg · hr; cusum-derived circadian alteration magnitude (CDCAM), 38.9 mm Hg. Panel b: Diastolic BP profile* (o) *and cusum plot* (−) *from the same subject. CPH, 199.9 mm Hg · hr; CDCAM, 44.8 mm Hg.*

Cusum-derived circadian alteration magnitude (CDCAM) quantifies the extent of the circadian pressure change. CDCAM is defined as the difference between cusum-derived crest and trough blood pressures and is calculated from the difference between the CPSs of the two periods:

CDCAM = crest CPS − trough CPS

Cusum plot height (CPH) (see "Appendix"), the difference between the maximum and minimum values of the plot, reflects circadian blood pressure alteration in terms of both extent and duration. Most ambulatory blood pressure profiles from both normotensive and hypertensive subjects follow a pattern similar to those of Figures 1 and 2. Blood pressure levels are highest during daytime hours, decline during the evening, fall markedly at night, and rise again the following morning. As a result, the maximum cusum plot value typically precedes the minimum value, and the time period intervening between maximum and minimum values is where the majority of interval pressures are below the mean 24-hour value. From this section of the plot, the difference between maximum and minimum values (CPH) can

be seen to equal the absolute value of the sum of the interval pressure deviations (from the mean value) multiplied by the interval durations, for all intervals of this time period (from maximum to minimum cusum values). The absolute value of the sum is used since the height of the plot cannot be negative. Alternatively, CPH may be calculated in Figures 1 and 2 from the two ascending sections of the plots, from zero to maximum value and from minimum value to zero. Thus, CPH also equals the sum of the interval pressure deviations multiplied by the interval durations for all intervals of these two periods. The resultant CPHs are therefore large if the time period between maximum and minimum values approximates 50% of the total duration of recording and the differences between interval pressures and the mean value are great.

Some ambulatory profiles show daytime falls and nocturnal rises in blood pressure (Figures 3 and 4). In the corresponding cusum plots, the maximum cusum value may still precede the minimum as in Figure 3, or the reverse may pertain as in Figure 4. Where the minimum value precedes the maximum, the value of CPH equals the absolute value of the sum of the products of the interval pressure deviations and the interval durations of either all the intervals during the period from minimum to maximum values or all the intervals during the two periods from zero to minimum value and from maximum value to zero. Again CPH is large where the sustained pressure differences from the mean value are large or prolonged, and CPH is small where pressure differences are small or poorly sustained.

Mean Daytime and Mean Nighttime Pressures and Mean Day–Night Pressure Difference Calculation

These pressures are calculated using assumed fixed daytime and nighttime periods. Mean daytime blood pressure is taken as the mean value of time-weighted pressure measurements from 9 AM to 8:59 PM and mean nighttime blood pressure as the time-weighted mean of measurements from 1 AM to 6:59 AM. The mean day–night pressure difference is calculated as mean daytime minus mean nighttime blood pressure.

Statistical Analysis

Statistical analyses were performed with SAS software (SAS Institute Inc., Cary, N.C.). Data are given as mean±SD. Statistical differences were evaluated using Student's t test for paired data. Pearson's method for regression equations was used as was the British Standards Institution repeatability coefficient (twice the standard deviation of differences between the pairs of repeated measurements).[23] To evaluate the agreement between paired measurements so as to allow comparisons between various statistics, each repeatability coefficient was also expressed as a fraction of estimated maximal biological variation of a given measurement (i.e., four times the standard deviation). Blood pressure variability was assessed by the root of the mean squared successive differences.[24]
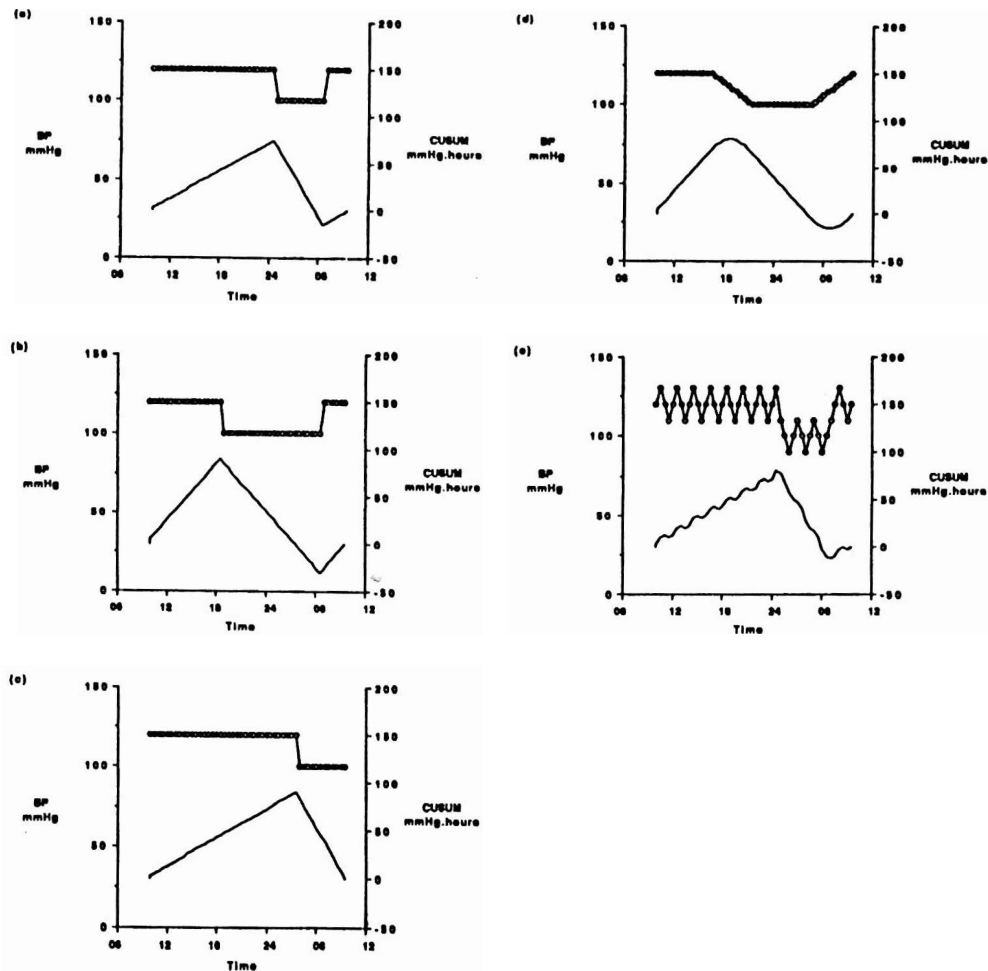
FIGURE 5. Panels a, b, c, d, and e: *Five hypothetical systolic blood pressure (BP) profiles* (o) *and their corresponding cumulative sums (cusum) plots* (−).

Results

The advantages of the cusum-derived statistics over previous measures of circadian blood pressure rhythm that use fixed day/night timing are illustrated in Figures 5A–5E and Table 1. Hypothetical systolic blood pressure profiles with corresponding cusum plots are shown in Figures 5A–5E. Statistics quanti-

fying blood pressure levels and circadian changes are presented in Table 1. The extent of the circadian pressure change is similar in each profile. However, the profiles do differ in terms of timing and total duration of the pressure alterations. The statistic CDCAM reflects the consistency of circadian rhythm between the profiles (Table 1), the decline in blood

TABLE 1. Statistics Quantifying Blood Pressure Levels, Circadian Patterns, and Blood Pressure Variability, Calculated for the Systolic Profiles of Figure 5

Statistic	Profile a	Profile b	Profile c	Profile d	Profile e
Mean 24-hour BP (mm Hg)	115.0	110.0	115.0	110.0	115.0
Mean daytime BP (mm Hg)	120.0	116.7	118.3	116.9	120.0
Mean nighttime BP (mm Hg)	100.0	100.0	110.0	101.6	100.0
Mean day–night difference (mm Hg)	20.0	16.7	8.3	15.3	20.0
Cusum-derived crest BP (mm Hg)	120.0	120.0	120.0	120.0	120.0
Cusum-derived trough BP (mm Hg)	100.0	100.0	100.0	100.0	100.0
Cusum-derived circadian alteration magnitude (mm Hg)	20.0	20.0	20.0	20.0	20.0
Cusum plot height (mm Hg·hr)	90.0	120.0	90.0	95.0	92.5
Root mean squared successive differences (mm Hg)	4.1	4.1	4.1	1.3	10.0

BP, blood pressure; cusum, cumulative sums.

TABLE 2.   Reproducibility of Statistics Quantifying Blood Pressure Levels and Circadian Patterns for Both Systolic and Diastolic Pressures

Statistic	First study	Second study	r	p	RC	RC/MBV
Systolic BP						
Casual BP	163.9±13.5	159.2±15.8	0.42	0.053	31.8	0.64
Mean 24-hour BP	140.8±11.8	143.2±13.6	0.83	0.000	15.0	0.31
Mean daytime (9 AM–8:59 PM) BP	148.5±16.2	149.1±14.2	0.76	0.000	21.2	0.37
Mean nighttime (1 AM–6:59 AM) BP	126.8±9.5	130.8±15.2	0.57	0.006	25.1	0.57
Mean day–night difference	21.6±14.5	18.2±13.9	0.37	0.079	31.9	0.68
Cusum-derived crest BP	153.4±15.8	153.4±14.9	0.87	0.000	19.1	0.33
Cusum-derived trough BP	124.9±9.3	128.9±13.7	0.64	0.001	21.0	0.50
Cusum-derived circadian alteration magnitude	28.6±12.3	24.4±11.3	0.52	0.012	23.1	0.56
Cusum plot height (mm Hg · hr)	125.5±51.9	110.2±46.1	0.37	0.082	110.5	0.68
Diastolic BP						
Casual BP	98.0±6.1	95.5±6.4	0.62	0.002	10.8	0.48
Mean 24-hour BP	87.0±9.1	88.3±9.9	0.87	0.000	9.8	0.27
Mean daytime (9 AM–8:59 PM) BP	93.1±11.7	93.3±10.2	0.78	0.000	14.8	0.36
Mean nighttime (1 AM–6:59 AM) BP	75.7±7.7	78.5±11.4	0.72	0.000	15.9	0.45
Mean day–night difference	17.4±9.7	14.9±10.2	0.47	0.029	20.6	0.61
Cusum-derived crest BP	96.4±12.1	96.1±10.3	0.76	0.000	15.8	0.37
Cusum-derived trough BP	74.7±7.9	76.7±10.2	0.73	0.000	14.1	0.42
Cusum-derived circadian alteration magnitude	21.8±10.0	19.4±8.2	0.49	0.023	18.7	0.60
Cusum plot height (mm Hg · hr)	96.4±41.2	90.4±35.2	0.46	0.032	80.2	0.61

Values are mean±SD; $n=22$; units are millimeters of mercury except where otherwise indicated. *r*, Correlation coefficient; *p*, denotes the significance of *r*; RC, repeatability coefficient; RC/MBV, repeatability coefficient/maximal biological variation; BP, blood pressure; cusum, cumulative sums.

pressure being calculated as 20 mm Hg in each. By contrast the mean day–night pressure difference, as calculated from fixed time periods for these systolic pressure profiles, ranges from 8.3 mm Hg to 20.0 mm Hg. When the high and low blood pressure periods do not coincide with the anticipated fixed day and night timings, the true daytime elevated pressure tends to be underestimated, the true nocturnal low blood pressure overestimated, and the circadian change tends to be underestimated. The height of the cusum plot is highest in Figure 5B, reflecting the more prolonged duration of pronounced pressure alterations. Figure 5E illustrates the ability of cusum methodology to quantify circadian rhythm independent of blood pressure variability.

Table 2 summarizes the calculated blood pressure levels and circadian pattern magnitudes using both fixed time periods and cusums techniques for both systolic and diastolic blood pressure on the repeated ambulatory blood pressure studies from the 22 hypertensive subjects. Using Student's *t* test for paired data, there were no significant differences in casual blood pressure, 24-hour mean ambulatory blood pressure, mean daytime, mean nighttime, or crest and trough blood pressure as recorded in the first and second assessments. In addition, circadian patterns as quantified by mean day–night difference, CDCAM and CPH did not differ between the two recordings. It may be seen that, for both systolic and diastolic blood pressures, mean daytime is less than crest blood pressure and mean nighttime greater

than trough blood pressure. This arises from dilutional effects of daytime blood pressure by nighttime levels and vice versa when fixed time periods are used. It also results in an underestimation of true circadian change as seen from the greater values of CDCAM compared with mean day–night difference.

Table 2 also shows the correlation coefficients and their significance, the repeatability coefficients, and the repeatability coefficients divided by maximal biological variation. Comparison of the correlation coefficients and the repeatability coefficient/maximal biological variation quotients shows that diastolic statistics are more reproducible than systolic, mean 24-hour ambulatory pressures are more reproducible than casual blood pressures, and, for systolic blood pressure, cusum-derived crest pressures, trough pressures, and CDCAMs are more reproducible than the corresponding mean daytime pressures, mean nighttime pressures, and mean day–night differences.

Discussion

Continuous monitoring of blood pressure throughout the day reveals a characteristic circadian pattern.[1,2,25] Furthermore, in normotensive and hypertensive subjects previous studies have shown that circadian patterns tend to be consistent between 24-hour study periods.[3-5] A nondipping circadian blood pressure pattern in hypertensive patients has been associated with a greater prevalence of left ventricular hypertrophy[6,7] and vascular complications[6,10] including stroke, peripheral vascular disease,

and carotid artery disease. There is at least the theoretical possibility that patients with an extreme dipping pattern may be at greater risk from nocturnal cardiac ischemia.[11,12] To clarify these possible associations between deviations from usual circadian rhythmicity and cardiovascular risk and also to examine for effects of antihypertensive therapy on circadian blood pressure patterns, precise quantification of the extent of the nocturnal blood pressure decline is essential.

Several statistical methods have been proposed for the analysis of circadian blood pressure recordings. Halberg's cosinor method[14,15] and subject-specific linear models[16] apply a smoothing process whereby a cosine curve with fixed frequency of 1 cycle/day is fitted to the data. This model implies an exactly symmetrical behavior of high and low blood pressure periods, both assumed to be of the same length, shape, and amplitude. In real profiles, however, the ratio of low to high blood pressure periods is usually about 8 to 16 with corresponding asymmetrical shape and amplitude characteristics. The model rigidly fixes the difference between acrophase and bathyphase at 12 hours, an assumption that does not fit empirical data.

A nonparametric approach based on a periodic spline model, fitted by robust multivariate regression techniques, as proposed by Streitberg and colleagues,[17] avoids these rigid assumptions and allows for multiphasic and asymmetrical profiles. Smooth curves are produced that closely follow the general trend of the original profile. Unfortunately, the model is complex and curve fitting is not feasible with standard statistical packages. The model allows testing for the presence of a circadian rhythm; simultaneous confidence intervals can be plotted, and if a straight horizontal line can be passed through the confidence band without crossing the boundaries, the rhythm is judged to be noncircadian. Thus, although this model has considerable advantages for qualitative analysis, quantitative analysis of circadian blood pressure is preferably obtained from original data, rather than from complex, possibly overmodeled smoothed profiles.

Measures of circadian blood pressure patterns derived from original data have included the range between the highest and lowest blood pressures and the difference and percent difference between average daytime and nighttime blood pressure.[6,7,10,13] Assessments of reproducibility and treatment effects have concentrated on the differences between daytime and nighttime means and multiple comparisons across shorter periods of the day.[4,5,25,26] Errors are thereby introduced because of intersubject and intrasubject variability in the timing of sleep/inactivity periods and their duration.

Our modification of the cusums technique allows construction of cusum plots from raw data that have not been remodeled. The slope of the plot over any given time period (the change in the cusum over that period divided by the period duration) indicates the average deviation of blood pressure from mean 24-hour blood pressure during that period. Both short-lived (siesta time, postprandial, or exertion related) and more prolonged changes in blood pressure may be readily appreciated from the plot as slope deviations. The plot facilitates the calculation of crest and trough blood pressures (the blood pressures of the 6-hour periods of highest and lowest pressures, respectively) and the derivation of two measures of circadian blood pressure alteration, CPH and CDCAM.

As blood pressures are usually highest during daytime hours and lowest nocturnally, cusum-derived crest and trough blood pressures approximate the mean daytime and mean nighttime pressures of previous studies.[6,7,10,13] The great advantage of cusum-derived pressures over those measures using fixed time periods is their lack of dilutional errors when subjects exhibit phase shifts in their sleeping/awake or inactive/active periods, or when these periods vary in duration. Additionally, because cusum-derived pressures do not assume the timing of the lowest and highest pressures, they remain meaningful when applied to the ambulatory profiles of shift workers.

CPH reflects both the extent and the duration of the circadian alteration. This statistic may be of particular value in studying the consequence of a nondipping circadian rhythm for end-organ involvement in hypertension.[6,7,10] If continuous pressure elevation contributes to the development of greater cardiovascular damage in patients with a nondipping circadian rhythm, then it is likely that the duration as well as the extent of any change in blood pressure is of importance.

CDCAM quantifies the extent of blood pressure change independent of the timing and duration of inactive or sleep periods. It is insensitive to short-lived blood pressure variability. The statistic is not subject to inaccuracies that are due to dilution of the trough period with higher blood pressure values, or to dilution of the crest period by lower blood pressure values. These dilutional effects result in an underestimation of the circadian pressure change by statistics, such as the mean day–night pressure difference, which are calculated from fixed time periods.

Blood pressure level varies considerably with time. Spontaneous changes in pressure on the order of 25% commonly occur,[26,27] and in the presence of a physician blood pressure rises even further.[28,29] This explains the relatively poor reproducibility of casual blood pressure measurement.[29] The enhanced reproducibility of 24-hour ambulatory blood pressures results from averaging of multiple readings.[29-32] Reduction of the number of readings contributing to the average increases the magnitude of the confidence interval for the estimate, which reduces measurement accuracy and reproducibility.[31] This explains the lower reproducibility of mean daytime, mean nighttime, crest, and trough blood pressure by comparison with the mean 24-hour value. The even poorer reproducibility of the measures of circadian pattern is to be expected since wider confidence

intervals would be anticipated for measures that are derived from differences between mean daytime and mean nighttime blood pressure or from differences between crest and trough blood pressure. Increased frequency of blood pressure recording could narrow the confidence intervals and would probably increase precision and reproducibility of all these statistics that measure blood pressure and its patterns. However, this possible gain would have the disadvantage of greater patient intrusion.

Interestingly, CDCAM, which has one third fewer contributory blood pressure recordings than the mean day–night pressure difference statistic, was as reproducible for diastolic and more reproducible for systolic blood pressure levels and circadian rhythm. This enhanced reproducibility, probably due to the lack of dilutional inaccuracies previously discussed, should enable any association between deviations from usual circadian rhythmicity and risk of target organ damage, morbidity, or mortality to be more powerfully detected. Similarly, drug effects on circadian patterns may be more sensitively analyzed.[33]

In conclusion, our study illustrates how a modification of cusum methodology may be applied to data obtained by automated noninvasive ambulatory blood pressure monitoring. The CPS facilitates perception of blood pressure changes. The CPH is a measure of pressure alteration extent and duration. CDCAM quantifies the extent of the pressure change independent of time with greater precision than previous measures. This approach may be a useful addition to current methods for analyzing blood pressure profiles.

Appendix

Mean 24-hour blood pressure was calculated as the sum of the products of interval pressures (mm Hg) and interval durations (hr) divided by the total duration of ambulatory monitoring (hr):

$$\text{mean 24-hour BP} = \frac{1}{D} \sum_{i=1}^{n} (BP_i)(d_i)$$

where D is total duration of ambulatory recording, n is total number of intervals, BP_i is blood pressure (systolic or diastolic of the ith interval), and d_i is i^{th} interval duration.

Cusum plot slope (CPS) was calculated as

$$CPS = \frac{CS_E - CS_B}{d_P}$$

where CS_E is cumulative sum at end of period, CS_B is cumulative sum at beginning of period, and d_P is duration of period.

Cusum plot height (CPH) was calculated as

$$CPH = \left| \sum_{i=1}^{n} (BP_i - \text{mean 24-hour BP})(d_i) \right|$$

where n is number of intervals between maximum cumulative sum and minimum cumulative sum (or between minimum and maximum cumulative sum values where the minimum value precedes the maximum), BP_i is blood pressure of the ith interval, and d_i is i^{th} interval duration.

References

1. Littler WA, Honour AJ, Carter RD, Sleight P: Sleep and blood pressure. *Br Med J* 1975;3:346–348
2. Pickering TG, Harshfield GA, Kleinert HD, Blank S, Laragh JH: Blood pressure during normal daily activities, sleep and exercise: Comparison of values in normal and hypertensive subjects. *JAMA* 1982;247:992–996
3. Gould BA, Mann S, Davies AB, Altman DG, Raftery EB: Can placebo therapy influence arterial blood pressure? *Clin Sci* 1981;61:478S–482S
4. Weber MA, Drayer JIM, Wyle FA, De Young JL: Reproducibility of the whole-day blood pressure pattern in essential hypertension. *Clin Exp Hypertens[A]* 1982;4:1377–1390
5. Weber MA, Drayer JIM, Nakamura DK, Wyle FA: The circadian blood pressure pattern in ambulatory normal subjects. *Am J Cardiol* 1984;54:115–119
6. Kobrin I, Oigman W, Kuman A, Ventura HO, Messerli FH, Frohlich ED, Dunn FG: Diurnal variation of blood pressure in elderly patients with essential hypertension. *J Am Geriatr Soc* 1984;32:896–899
7. Verdecchia P, Schillaci C, Guerrieri M, Gatteschi C, Benemio G, Boldaini F, Porcellati C: Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension. *Circulation* 1990;81:528–536
8. Gosse P, Campello G, Roudaut R, Dallocchio M: High night blood pressure in treated hypertensive patients: Not harmless. *Am J Hypertens* 1988;1:195s–198s
9. Tochikubo O, Ochiai H, Oota T, Miyajima E, Kaneko Y: Measurement of base blood pressure during sleep and its clinical significance in hypertensive patients. *Jpn Circ J* 1987; 51:1174–1183
10. O'Brien E, Sheridon J, O'Malley K: Dippers and non-dippers (letter). *Lancet* 1988;2:397
11. Floras JS: Antihypertensive treatment, myocardial infarction and ischaemia. *Lancet* 1988;2:944–946
12. O'Brien E, O'Malley K: Overtreating hypertension (letter). *Br Med J* 1988;297:1607
13. Valty J, Le Heuzey JY, Buoncuone A, Sagnes JY, Cohen A, Scala PJ: Etude des variation nycthemerales de la pression arterielle chez les sujets hospitalises. *Arch Mal Coeur* 1989;82: 1039–1042
14. Halberg F: Chronobiology. *Annu Rev Physiol* 1969;31:675–725
15. Smolensky M, Tatan SE, Bergman S, Losman J, Barnard CN, Dacso CC, Kraft IA: Circadian rhythmic aspects of human cardiovascular function: A review by chronobiologic statistical methods. *Chronobiologia* 1975;3:337–371
16. Marler MR, Jacob RG, Lehoczky JP, Shapiro AP: The statistical analysis of treatment effects in 24-hour ambulatory blood pressure recordings. *Stat Med* 1988;7:697–716
17. Streitberg B, Meyer-Sabellek W, Baumgart P: Statistical analysis of circadian blood pressure recordings in controlled clinical trials. *J Hypertens* 1989;7(suppl 3):S11–S17
18. Wohl H: The cusum plot: Its utility in the analysis of clinical data. *N Engl J Med* 1977;296:1044–1045
19. De Saintonge DMC, Vere DW: Why don't doctors use cusums? *Lancet* 1974;1:120–121
20. O'Brien E, Perry I, Sheridan J, Atkins N, O'Malley K Application of cusums to ambulatory blood pressure data: A simple statistical technique for detecting trends over time *J Hypertens* 1989;7:707–709
21. BHS recommendations for blood pressure measurement. *Br Med J* 1986;293:611–615
22. O'Brien E, Mee F, Atkins N, O'Malley K: Evaluation of the SpaceLabs 90202 non-invasive ambulatory recorder according

to the AAMI standard and BHS criteria. *J Hum Hypertens* 1991;5:223–226

23. British Standard Institution: Precisions of test methods: Guide for the determination and reproducibility for a standard test method (BS 5497, part I). London BSI, 1979

24. Schachinger N, Langewitz W, Schmieder RE, Ruddel H: Comparison of parameters for assessing blood pressure and heart rate variability from non-invasive twenty-four-hour blood pressure monitoring. *J Hypertens* 1989;7(suppl 3):S81–S84

25. Drayer JIM, Weber MA, De Young JL, Wyle FA: Circadian blood pressure patterns in ambulatory hypertensive patients. *Am J Med* 1982;73:493–499

26. Richardson DW, Honour AJ, Fenton GW, Stott FH, Pickering GW: Variation in arterial pressure throughout the day and night. *Clin Sci* 1964;26:445–460

27. Bevan AT, Honour AJ, Stott FH: Direct arterial pressure recording in unrestricted man. *Clin Sci* 1986;36:329–334

28. Ayman D, Goldshine AD: Blood pressure determinations by patients with essential hypertension: The difference between clinic and home readings before treatment. *Am J Med Sci* 1940;200:465–474

29. Mancia G, Bertinieri G, Grassi G, Parati G, Pomidossi G, Ferrari A, Gregorini L, Zanchetti A: Effects of blood pressure measurement by the doctor on patient's blood pressure and heart rate. *Lancet* 1983;2:695–697

30. James JD, Pickering TG, Yee LS, Harshfield GA, Riva S, Laragh JH: The reproducibility of average ambulatory, home, and clinic pressures. *Hypertension* 1988;11:545–549

31. Conway J, Johnson J, Coats A, Somers V, Sleight P: The use of ambulatory blood pressure monitoring to improve accuracy and reduce the numbers of subjects in clinical trials of antihypertensive agents. *J Hypertens* 1988;6:111–116

32. Fitzgerald DJ, O'Malley K, O'Brien ET: Reproducibility of ambulatory blood pressure recordings, in Weber MA, Drayer JIM (eds): *Ambulatory Blood Pressure Monitoring.* New York, Springer-Verlag New York, Inc, 1984, pp 71–74

33. Sirgo MA, Mills RJ, De Quattro V: Effects of antihypertensive agents on circadian blood pressure and heart rate patterns. *Arch Intern Med* 1988;148:2547–2552