Diurnal Blood Pressure Change Varies With Stroke Subtype in the Acute Phase

Suzanne L. Dawson, MRCP; Steve N. Evans, MRCP; Bradley N. Manktelow, MSc; Martin D. Fotherby, MD; Thompson G. Robinson, MD; John F. Potter, DM

**Background and Purpose**—It is unclear whether acute stroke is associated with a loss of the normal diurnal blood pressure (BP) change and whether stroke type influences this. Some of this confusion results from the use of fixed time definitions of day and night, which can be overcome by the use of cumulative sums analysis (cusums).

**Methods**—Ninety-eight stroke patients had 24-hour BP monitoring (Spacelabs 90207) performed within 48 hours of ictus. Three subgroups were identified: cortical infarct, n = 50; subcortical infarct, n = 29; and primary intracerebral hemorrhage [PICH], n = 19. An age-matched control group of 74 subjects was also studied. Diurnal change was assessed by both day-night differences (absolute and percentage) and cusums (cusums plot height [CPH] and circadian alteration magnitude [CDCAM]): ANCOVA was used to compare groups.

**Results**—Compared with control subjects, cortical infarct and PICH subgroups had significantly reduced mean diurnal systolic changes using day-night differences (absolute, −12 and −17 mm Hg; percentage, −10 and −12, respectively; \( P < 0.0001 \)) and cusums (CDCAM, −6.96 and −8.6 mm Hg; CPH, −32.05 and −46.04 mm Hg, respectively; \( P < 0.005 \)), only the subcortical infarct subgroup demonstrated reduced percentage differences (−4.4%, \( P < 0.02 \)). Mean diastolic differences were significantly reduced in all stroke subgroups (CPH, −24.84, −17.31, and −36.92 mm Hg; absolute, −8.26, −4.04, and −11.44 mm Hg; percentage, −10.65, −5.81, and −15.23%, for cortical infarct, subcortical infarct, and PICH subgroups, respectively; \( P < 0.05 \)), except for CDCAM, which was not reduced in subcortical infarcts (−4.78 and −7.70 mm Hg for cortical infarct and PICH subgroups, respectively; \( P < 0.001 \)).

**Conclusions**—Diurnal BP change was reduced in the 3 stroke subgroups studied, especially in patients with cortical infarcts and PICH. This may reflect damage to the central modulation of autonomic BP control. The implications in terms of prognosis and therapy in the acute period require further study. (Stroke. **1998;29:1519-1524**.)

**Key Words:** analysis, cumulative sums • blood pressure • circadian rhythm • stroke, acute

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...demonstrated a loss of diurnal rhythm in a group of 86 patients studied within 12 hours of acute stroke, and stated that stroke patients could be considered to be nondippers. The prognostic significance of nondipping following acute stroke is unclear, but some preliminary data from our department imply an association between reduced day-night change and poor outcome.9,12

A number of definitions have been used to define dipping, including an absolute 10 mm Hg day minus night SBP fall17,18 or a 10% SBP decrease; the prevalence of nondipping varies substantially according to the definition adopted.19 Furthermore, dipping status is defined following a fixed time period definition of day and night,19 which incorrectly assumes that all subjects are awake and asleep at these predetermined times. Indeed, Wong Chung et al20 reported that the prevalence of dipping varied between 22% and 61%, depending on the time period used to define night. However, any classification of dippers and nondippers is arbitrary, because diurnal
BP variation is normally distributed, and it is therefore preferable to consider day-night differences as a continuous variable. However, a number of statistical methods have been used to improve the description of diurnal BP variation. In particular, cusums-derived statistics have been used as a simple method of quantitatively analyzing diurnal BP profiles and have been shown to improve the reproducibility of diurnal SBP variation. Some preliminary work from our department using this technique implies that there may not be a significant difference between acute stroke patients and control subjects regarding diurnal BP change, but stroke subtype was not considered in this study. Therefore, the aims of the current study were to assess whether there were differences in the diurnal BP change between acute stroke patients and an age-matched control group (using both fixed-time diurnal change and cusums analysis) and, further, to investigate the possible influence of stroke subtype on this change.

Subjects and Methods

Subjects
Patients admitted to 2 of the Leicester teaching hospitals within 24 hours of stroke onset were studied. We included in the study patients who had a CT-confirmed diagnosis within 10 days of the event, and we subsequently divided them into cerebral infarcts (either total anterior circulation or partial anterior circulation syndromes, or lacunar syndromes, according to the Oxfordshire Community Stroke Project classification, using CT scan results and the findings of neurological examination performed by S.L.D. and T.G.R. independently on the same day) or PICHs. Antihypertensive treatment was stopped on admission, as per hospital protocol, and patients were taking no other medications known to influence the cardiovascular or autonomic nervous systems. Patients with a history of autonomic impairment, diabetes mellitus, atrial fibrillation, chronic illness leading to functional dependence, or diminished consciousness level (as defined by the National Institutes of Health Stroke Scale) were excluded from the study.

Control subjects were recruited from community-based respondents to a local newspaper advertisement calling for volunteers and from elective orthopedic surgical and nonacute medical inpatients. All control subjects were independent in their activities of daily living and free from cardiovascular and cerebrovascular disease as determined by history, physical examination, and 12-lead ECG. All subjects (or their caregivers) gave informed consent, and the study was approved by the Leicestershire Hospitals’ Ethical Committee.

Study Protocol
Casual supine BP measurements (diastolic phase V) were recorded on 3 occasions in all subjects using a standard mercury sphygmomanometer and an appropriately sized cuff. Twenty-four-hour BPM was performed using a Spacelabs model 90207 recorder. The accuracy of this device has already been established and approved by the British Hypertension Society. The monitor was programmed to record at 15-minute intervals between 7:00 AM and 11:00 PM and at 30-minute intervals between 11:01 PM and 6:59 AM. Initially the 24-hour BP monitor was calibrated against the casual readings; if there was >5 mm Hg discrepancy between the two methods, the subject was excluded from the study. Data were downloaded onto an IBM-compatible personal computer for further analysis, and patients were excluded at this stage if <80% data capture had been achieved. Data were automatically edited to exclude nonphysiological readings.

Casual and ambulatory BP readings were made on the same day, and in the study group were completed within 48 hours of the ictus.

Statistical Methods
Casual BP values were taken as the mean of the 3 consecutive readings. The mean 24-hour day (7:00 AM to 11:00 PM) and night (11:01 PM to 6:59 AM) values were noted. The differences between mean day and night SBP and DBP values (day–night) were calculated (DNSBP and DNDBP, respectively) as absolute (mean day–mean night) and percentage ([mean day–mean night] ÷ mean day) changes.

To avoid the discrepancies caused by arbitrary definitions of day and night, the diurnal BP profile was quantitatively analyzed using cusums-derived statistics. To calculate the systolic cusums mean 24-hour SBP, pressure was taken as the reference value and subtracted from each time-weighted SBP value. The resulting values are summed in sequence and plotted against time to form a modified cusums plot (see Figure 1). The slope of the plot (CPH) during the 6-hour period ascending and night, the diurnal BP profile was quantitatively analyzed using cusums-derived statistics. The accuracy of this device has already been established and approved by the British Hypertension Society.

Figure 1. Modified cusums plot to illustrate calculation of CPH and CDCAM for SBP. For further explanation see text.
Results
We studied 98 acute stroke patients (62 men), mean age 71.2 ± 10.3 years (range, 39 to 89 years), and an age- and sex-matched control group of 74 healthy volunteers (42 men), mean age 69.1 ± 7.0 years (range, 48 to 84 years). The stroke subjects were then subclassified into cortical infarcts (n = 50; 31 men; mean age, 71.2 ± 9.8 years) and subcortical infarcts (n = 29; 22 males; mean age, 70 ± 11 years) and PICH (n = 19; 9 men; mean age, 73.2 ± 10.5 years). Baseline BP and HR characteristics are shown in Table 1. Mean 24-hour BP profiles for the four groups are illustrated in Figure 2.

Day-Night Differences
Using a definition of a 10 mm Hg fall in SBP to indicate the presence of dipping,17,18 84% controls, 28% cortical strokes, 62% subcortical strokes, and 20% of PICHs fulfilled these criteria; however, a definition of a 10% SBP fall1 led to values of 61%, 16%, 45%, and 5%, respectively. If changes in DBP were used instead (ie, 5 mm Hg fall or 10% fall),17,18 results of 92%, 50%, 79%, and 30% or 81%, 26%, 55%, and 15% were found for control subjects, the cortical infarct group, the subcortical infarct group, and PICHs, respectively.

Mean absolute and percentage day-night differences for both SBP and DBP are shown in Table 2. Results of the mean differences between the control and stroke subgroups are presented in Table 3; day-night differences are age-adjusted, since this was identified as a significant covariate.

For systolic day-night differences there was a significant reduction in mean absolute DNSBP between control subjects and cortical infarct and PICH subgroups (–12 and –17 mm Hg, respectively; \( P < 0.0001 \)). However, percentage DNSBP was significantly reduced in all 3 subgroups (–9.1%, –12.1%, \( P < 0.001 \), and –4.4%, \( P < 0.02 \), for cortical infarct, PICH, and subcortical infarct subgroups, respectively).

Diastolic day-night differences, whether calculated using absolute or percentage differences, were significantly reduced in all 3 stroke subgroups compared with control subjects (absolute DNDBP, –8, –4, and –11 mm Hg, \( P < 0.001 \); percentage DNDBP, –10.7%, –5.8%, and –15.2%, \( P < 0.05 \), for cortical infarct, subcortical infarct, and PICH subgroups, respectively).

Cusums Analysis
Mean values of CDCAM and CPH for each group are shown in Table 2; the differences between groups are shown in Table 3.
Systolic CDCAM and CPH were significantly reduced in the cortical infarct and PICH subgroups compared with control subjects (CDCAM −7.0 and −8.6 mm Hg and CPH −32.05 and −46.04 mm Hg for cortical infarct and PICH subgroups, respectively, *P*<0.005); there was no significant difference between control subjects and the subcortical infarct group. These changes persisted even after possible differences in baseline characteristics between the groups were controlled for. The difference in cusums results for the subcortical infarct group (i.e., significant reduction in CPH but not CDCAM) is interesting, because CDCAM is considered insensitive to short-term BP changes whereas CPH is believed to indicate these changes and to be of prognostic value in predicting end-organ damage in hypertensive subjects.24

Previous studies of the diurnal BP change poststroke have reported a reduced day-night difference,10–14,16 although these were largely uncontrolled studies11,13,16 and they did not assess the influence of stroke subtype. There are a number of possible explanations for the reported difference in the diurnal BP change following acute stroke. First, this may be related to the actual BP levels because after stroke 20% of the hypertensive population no longer have diurnal BP changes.4 BP levels are commonly raised in the acute stroke period,31–33 particularly in patients of Afro-Caribbean decent,16 although we are unable to comment on racial differences because our study population contained only 4 patients of Asian decent. Although the significant differences in diurnal BP change we describe persisted after controlling for possible confounding differences, the only significant covariate.

**Discussion**

The present study has demonstrated a reduction in diurnal BP change in acute stroke patients compared with control subjects that is related to stroke subtype. Diurnal SBP change, whether assessed by cusums (CDCAM, CPH) or absolute or percentage day-night difference, is significantly reduced in patients with cortical infarcts and PICH, but only percentage differences are reduced in those with subcortical infarcts compared with control subjects. Diurnal DBP change, assessed by the same methods, is significantly altered in all subgroups measured, except CDCAM in the subcortical infarct group. These changes persisted even after possible differences in baseline characteristics between the groups were controlled for. The difference in cusums results for the subcortical infarct group (i.e., significant reduction in CPH but not CDCAM) is interesting, because CDCAM is considered insensitive to short-term BP changes whereas CPH is believed to indicate these changes and to be of prognostic value in predicting end-organ damage in hypertensive subjects.24

**TABLE 2. Measures of Diurnal Blood Pressure Changes in Controls and Stroke Groups**

<table>
<thead>
<tr>
<th>SBP results</th>
<th>Controls</th>
<th>Cortical Infarct</th>
<th>Subcortical Infarct</th>
<th>PICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNSBP change, mm Hg</td>
<td>17±10</td>
<td>5±12</td>
<td>12±9</td>
<td>−1±15</td>
</tr>
<tr>
<td>DNSBP change, %</td>
<td>12.3±6.9</td>
<td>2.9±7.5</td>
<td>7.8±5.7</td>
<td>−0.4±9.5</td>
</tr>
<tr>
<td>Circadian alteration magnitude SBP, mm Hg</td>
<td>23.3±8.1</td>
<td>19.6±9.9</td>
<td>23.7±7.8</td>
<td>19.6±10.2</td>
</tr>
<tr>
<td>CPH SBP, mm Hg</td>
<td>109±38.2</td>
<td>92±48.1</td>
<td>105±33</td>
<td>86±46.6</td>
</tr>
</tbody>
</table>

**DBP results**

<table>
<thead>
<tr>
<th>DBP results</th>
<th>Controls</th>
<th>Cortical Infarct</th>
<th>Subcortical Infarct</th>
<th>PICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNDBP change, mm Hg</td>
<td>13.2±7.8</td>
<td>5±8</td>
<td>9±6</td>
<td>1±9.7</td>
</tr>
<tr>
<td>DNDBP change, %</td>
<td>16.5±7.8</td>
<td>5.5±8.7</td>
<td>10.6±6.3</td>
<td>0.6±10.5</td>
</tr>
<tr>
<td>Circadian alteration magnitude DBP, mm Hg</td>
<td>17.4±5.4</td>
<td>14.0±6.2</td>
<td>16.3±5.6</td>
<td>13.2±4.3</td>
</tr>
<tr>
<td>CPH DBP, mm Hg</td>
<td>82.3±27.3</td>
<td>63.7±30.2</td>
<td>71.2±24.1</td>
<td>60.8±19.4</td>
</tr>
</tbody>
</table>

* Minus sign indicates nocturnal rise in BP. Data are mean±SD.

**TABLE 3. Adjusted Mean Differences Between Stroke Subtypes and Control Group**

<table>
<thead>
<tr>
<th>Diurnal Measurement</th>
<th>Cortical Infarcts</th>
<th>Subcortical Infarct</th>
<th>PICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute DNSBP</td>
<td>−11.7 (−16.52, −6.93)*</td>
<td>−4.98 (−10.69, 0.74)</td>
<td>−16.51 (−23.28, −9.75)*</td>
</tr>
<tr>
<td>Absolute DNDBP</td>
<td>−8.26 (−11.42, −5.09)*</td>
<td>−4.04 (−7.82, −0.27)*</td>
<td>−11.44 (−15.91, −6.97)*</td>
</tr>
<tr>
<td>Percentage DNSBP</td>
<td>−9.08 (−12.21, −5.95)*</td>
<td>−4.40 (−8.14, −0.67)*</td>
<td>−12.05 (−16.47, −7.63)*</td>
</tr>
<tr>
<td>Percentage DNDBP</td>
<td>−10.65 (−14.21, −7.09)*</td>
<td>−5.81 (−10.05, −1.56)*</td>
<td>−15.23 (−20.25, −10.21)*</td>
</tr>
<tr>
<td>CDCAM SBP</td>
<td>−6.96 (−10.94, −2.98)*</td>
<td>−1.98 (−6.49, 2.52)</td>
<td>−8.60 (−14.43, −2.77)*</td>
</tr>
<tr>
<td>CDCAM DBP</td>
<td>−4.78 (−7.28, −2.28)*</td>
<td>−2.55 (−5.48, 0.38)</td>
<td>−7.70 (−11.61, −3.78)*</td>
</tr>
<tr>
<td>CPH SBP</td>
<td>−32.1 (−50.7, −13.41)*</td>
<td>−15.0 (−36.06, 6.14)</td>
<td>−46.0 (−73.35, −18.72)*</td>
</tr>
<tr>
<td>CPH DBP</td>
<td>−24.84 (−37.01, −12.68)*</td>
<td>−17.3 (−31.55, −3.07)*</td>
<td>−36.92 (−55.94, −17.91)*</td>
</tr>
</tbody>
</table>

Results are adjusted mean differences (95% confidence intervals) between stroke subtypes and controls (mm Hg or %).

*Significant difference between group and control (*P*<0.05).
influences, including mean BP levels and age, both of which influence diurnal BP change. Other groups have also shown that subject demographics may influence short-term (ie, 30-minute) diurnal BP change or dipping.44

Second, these changes may reflect true differences related to stroke type (ie, cerebral infarct or intracerebral hemorrhage) or site of damage (ie, damage to the autonomic regulation centers of the cardiovascular system). Yamamoto et al44 reported a significant reduction in the percentage of nocturnal BP decline in subjects with subcortical and brainstem strokes, particularly those caused by PICH. They hypothesized that this reflected injury to the central autonomic nervous system, because there was only a weak correlation between SBP and HR. Lip et al16 have also shown this change with PICH and have suggested another possible influence, that of the Cushing response35 secondary to changes in intracranial pressure caused by edema; in most cases, however, the HR response does not support this theory. In keeping with the present study, Bryant et al12 reported a trend toward a reduced nocturnal fall in lacunar strokes, but the timing after the ictus was not standardized. Sander and Klingelhofer47 reported a reduction in diurnal change with thromboembolic infarction and the presence of a reversed dip in subjects with involvement of the insular cortex; this was associated with an increase in plasma norepinephrine levels, indicating an alteration in modulation of the sympathetic nervous system. Further evidence regarding the alteration of autonomic modulation following stroke has come from both rodent and human studies. Recently, experimentally induced middle cerebral artery occlusion has been shown to lead to an increase in renal sympathetic nerve activity, increased circulating catecholamine levels, and myocardial damage in Wistar rats, particularly if the right hemispheric insular cortex and amygdala regions were affected; spontaneously hypertensive rats and Wistar-Kyoto rats responded differently, however, which implies that both genetic constitution and stroke site influence cardiovascular modulation.37,38 Human studies have also demonstrated a lateralization of cardiovascular control, with the right hemisphere felt to be predominantly involved,39,40 especially regarding parasympathetic control,41 which is reduced in acute stroke but does show a gradual recovery with time.42

Third, arbitrary classification of day and night in previous studies may account for some of the conflicting results, because the use of fixed time periods assumes that all subjects have the same sleep and wake cycles, yet they are frequently disturbed in the elderly and hospitalized populations.43 Our study has overcome this by the use of the cusums analysis, which is both simple and reproducible.21,25,26

Whether this reduction in diurnal change has important prognostic implications is as yet unclear. In patients with essential hypertension, loss of diurnal change is certainly associated with an increased prevalence of target organ damage, including left ventricular hypertrophy,1,2,7 as well as a higher incidence of both cardiovascular and cerebrovascular complications.4,37,44 Ohkubo et al have recently reported a higher mortality rate in reverse dippers and nondippers.45 Preliminary work8,12 implies that this reduction in change is related to poor outcome in the stroke population. However, Nakamura et al46 looked at the recurrent stroke rate in 81 patients with chronic cerebrovascular ischemia and found no difference in recurrence between untreated hypertensive dippers and nondippers, although treated dippers had higher rates (12.5% versus 1.5% per patient-year), possibly implying either a treatment effect or impairment of cerebral autoregulation leading to episodes of cerebral hypoperfusion.

The question remains as to whether these BP changes are due to the stroke per se or associated factors, eg, underlying hypertension. Sander and Klingelhofer47 found that 15-minute diurnal SBP variability correlated with atherosclerosis of the internal carotid artery but not the external carotid artery, a possible mechanism for the finding by the same group of reduced BP variability in thromboembolic but not hemodynamic strokes.36 Imai et al14 described the diurnal BP change in a normal Japanese population and highlighted the influence of age and mean BP on this response through stiffening of the arterial tree and subsequent modulation of the autonomic nervous system; however, our results persisted even after we controlled for these factors. The alternative view, ie, that these changes are secondary to the stroke, is supported by Kario and Shimada,48 who reported the conversion of a dipper to a nondipper following lacunar stroke; Yamamoto et al,14 who followed some subjects longitudinally and found a further decline after repeat stroke episodes; and Korjelaainen et al,32 who reported the recovery of HR changes in the 6 months following the ictus.

There are some shortcomings to the present study. The application of the monitor was not at a fixed hour during the day, but none of the recordings were started at night; the arm used for attachment of the cuff was not standardized as the hemiplegic or unaffected arm in the patients or the dominant or nondominant arm in the control subjects, but there were no significant differences in casual BP measurements between the arms. No diary information was recorded by either patients or control subjects; consequently, we know little of the duration of sleep, but the use of cusums analysis should remove the need for this. Due to small patient numbers we were unable to more accurately study the influence of stroke site on results, but the classification we have used gives some information on site and underlying pathology.

In conclusion, the present study has demonstrated a significant reduction in diurnal SBP and DBP changes in acute stroke patients compared with control subjects, using a variety of different methods to measure this. The extent of the attenuation is related to stroke subtype, whether cortical or subcortical cerebral infarct or PICH. These differences are not explained by any difference in absolute BP levels and are not a consequence of fixed-time definition of day and night, as they are reproduced with the use of cusums analysis techniques. The underlying pathophysiological mechanism or mechanisms causing these changes are unclear, but may be related to damage to central integration of autonomic BP control. At present the prognostic implications of these findings are unclear and are the subject of further study. If there is an association between loss of diurnal change and poor outcome, it may be possible to identify an antihypertensive therapy that will improve clinical outcome, but any such intervention must take into consideration effects on cerebral
blood flow and autoregulation; for now we cannot recommend any change to clinical practice.

Acknowledgments
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References
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