Blood Pressure Evolution After Acute Ischemic Stroke in Patients With and Without Sleep Apnea

Claudia Selic, MD*; Massimiliano M. Siccoli, MD*; Dirk M. Hermann, MD; Claudio L. Bassetti, MD

Background and Purpose—Sleep apnea (SA) is an independent risk factor for arterial hypertension and is present in 50% to 70% of patients with ischemic stroke. The effects of SA on blood pressure (BP) and stroke outcome in the acute stroke phase are essentially unknown.

Methods—We studied 41 consecutive patients admitted within 96 hours after stroke onset. Stroke severity on admission (National Institutes of Health Stroke Scale [NIHSS]) and stroke outcome at discharge (modified Rankin Disability Scale [mRS]) were assessed. Nocturnal breathing was assessed with an ambulatory device the first night after admission. SA was defined by an apnea-hypopnea-index (AHI) ≥10/hour, and moderate-severe SA (MSSA) was defined by an AHI >30/hour. BP monitoring was performed during the first 36 hours after admission. A nondipping status (NDS) was defined by a ratio >0.9 of mean systolic BP during nights 1 to 2/mean systolic BP during day 2.

Results—SA was found in 28 (68%) and MSSA in 11 (27%) of 41 patients. A correlation was found between AHI and both NIHSS (r=0.331; P=0.035) and mRS (r=0.341; P=0.031). Patients with MSSA had higher systolic and diastolic BP values during night 1 (P=0.003), day 2 (P=0.004), and night 2 (P=0.03). NDS was found in 26 (63%) patients. Nondippers had a similar AHI but higher NIHSS (P=0.004) and mRS (P=0.005) than dippers. AHI and NDS were confirmed to be independent predictors for both stroke severity and stroke outcome in a multiple stepwise linear regression model.

Conclusions—SA severity is associated with high 24-hour BP values but only weakly with stroke severity and outcome. Conversely, NDS is linked with a more severe stroke and a poorer evolution but not with SA severity. These data suggest different, although overlapping, pathophysiological and clinical implications of circadian and nocturnal BP values in acute stroke. (Stroke. 2005;36:2614-2618.)

Key Words: blood pressure ■ dipping/nondipping ■ ischemic stroke ■ sleep apnea ■ stroke outcome

Sleep apnea (SA) is a well-recognized independent risk factor for cardiovascular morbidity and mortality.1–2 One possible cause for this link is the association of SA with arterial hypertension, which was found in several studies independently of gender, body weight, age, and other cardiovascular risk factors.3,4 The prevalence of SA in patients with arterial hypertension is higher compared with the normal population,5 and treatment with continuous positive airway pressure reduces blood pressure (BP) in hypertensive SA patients.6,7 Finally, SA is very frequent (50% to 70%) in patients with transient ischemic attack and acute stroke8–10 and may affect stroke outcome.11–13

Evolution of BP in acute stroke and its impact on outcome has been addressed in several studies. Eighty percent of patients with acute stroke are hypertensive on admission, and elevated BP spontaneously declines over the following days.14,15 Patients with both increased and decreased BP may have an unfavorable prognosis, suggesting a bell-shaped relationship between BP and stroke outcome.16,17 In addition, an impairment of circadian BP modulation with loss of physiological nocturnal BP dipping has been documented in the first days after stroke.18–21

Considering the strong association between SA and both hypertension and stroke and the impact of elevated BP levels on stroke outcome,19,22,23 it is surprising that the relationship among BP, SA, and stroke was studied only once in the literature.24 To test the hypothesis of a link between SA and high BP in acute stroke, we correlated BP values with SA severity and short-term outcome in 41 patients with acute ischemic stroke.

Methods

Patients

Forty-five consecutive patients (ages 18 to 85 years) with acute ischemic stroke admitted to our Department of Neurology were prospectively included. The study design was approved by the local ethical committee, and written informed consent was obtained from each patient or relatives. Patients with very severe strokes (National Institutes of Health Stroke Scale [NIHSS] ≥20), intracerebral/sub-
arachnoidal hemorrhage, hemorrhagic infarction, coma/stupor, and life-threatening medical conditions were excluded.

Clinical Evaluation
Cardiovascular risk factors including family history, arterial hypertension (BP >140/90 mm Hg measured ≥3 times before stroke), diabetes (fasting glucose level >140 mg/dL), smoking status, hypercholesterolemia (cholesterol level >250 mg/dL), adipositas (body mass index [BMI] ≥25 kg/m²), and previous history of coronary heart disease were recorded.

Stroke assessment included NIHSS and Scandinavian Stroke Scale (SSS). Short-term stroke outcome was estimated by the modified Rankin Disability Scale (mRS) at hospital discharge.

Nocturnal Breathing
Overnight respirography was performed with an ambulatory device (Autoset Embletta PDS; ResMed) during the first night after admission (night 1). This respirography has been validated before in patients with stroke (C.L.B., et al, unpublished data, 2005). The analysis was performed automatically and corrected manually. Apnea was defined by a cessation of oronasal airflow ≥10 seconds and hypopnea by a reduction of oronasal airflow ≥10 seconds by ≥50% or ≥30% when associated with an oxygen desaturation ≥4%. Apnea-hypopnea index (AHI) was defined by the mean number of apneas and hypopneas per hour and apnea index (AI) by the mean number of apneas per hour between lights off and on. Moderate-severe SA (MSSA) was defined by AHI >30/hour, mild SA by AHI 10 to 30/hour, and no SA by AHI <10/hour. A differentiation between obstructive (OAI) and central (CAI) AI was undertaken according to standard criteria. The percentage of time with oxygen saturation <90%, as well as the oxygen desaturation-index (ODI) were calculated. The magnitude of the oxygen desaturation considered for ODI was ≥4%. Body position was not monitored.

BP
BP and pulse rate were monitored with an ambulatory device (bp one, Cardiette) over 36 hours in intervals of 30 minutes beginning from night 1. Mean systolic and diastolic BP values and pulse rates were calculated in all of the patients for each period of time (night 1, day 2, and night 2, defined individually). NDS was defined as a ratio of mean systolic BP during nights 1 and 2/mean systolic BP day 2, and night 2, defined individually). NDS was defined as a ratio of mean systolic BP during nights 1 and 2/mean systolic BP day 2. The number of antihypertensive drugs used on admission were recorded.

Statistics
Statistical analysis was performed with the SPSS software package. Continuous data were presented as mean/SD and categorical variables as numbers/percentage. Student unpaired t tests were used for comparison of patients groups and for testing of continuous variables. Not normally distributed data were compared with the Mann–Whitney test. Correlations were calculated using the Pearson coefficient. A P<0.05 was considered to be statistically significant. Multiple stepwise regression models (with entry value set to 0.05 and removal value set to 0.1 in the univariate analysis) were tested using stroke severity (SSS at day 1) and stroke outcome (mRS) as dependent variables. Age, gender, number of cardiovascular risk factors, BMI, history of arterial hypertension, diabetes, smoking status, hypercholesterolemia, coronary heart diseases, adipositas, mean systolic BP night 1/day/night 2, mean diastolic BP night 1/day/night 2, mean pulse night 1/day/night 2, number of antihypertensive drugs, NDS, and AHI were candidate predictors.

Results
Forty-five patients were included, 41 completed the study, and 4 had to be excluded. The main demographic and clinical characteristics of these 41 patients are summarized in Table 1.

### Table 1. Main Results of All Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female (%)</td>
<td>33/8 (81/19)</td>
</tr>
<tr>
<td>Age, y</td>
<td>63±13 [25 to 83]</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27±4 [21 to 39]</td>
</tr>
<tr>
<td>NIHSS day 1</td>
<td>7±5 [1 to 20]</td>
</tr>
<tr>
<td>SSS day 1</td>
<td>41±13 [8 to 58]</td>
</tr>
<tr>
<td>Stroke side, right/left (%)</td>
<td>23/18 (56/44)</td>
</tr>
<tr>
<td>Hemiparesis/brainstem stroke (%)</td>
<td>38/3 (93/7)</td>
</tr>
<tr>
<td>Latency S-R, h</td>
<td>37±25 [8 to 96]</td>
</tr>
<tr>
<td>mRS at discharge</td>
<td>2±1.4 [0 to 5]</td>
</tr>
<tr>
<td>Duration of hospital stay, days</td>
<td>12±7 [3 to 31]</td>
</tr>
<tr>
<td>AHI, h/h</td>
<td>23±22 [0 to 101]</td>
</tr>
<tr>
<td>OAI, h/h</td>
<td>11±6 [0 to 70]</td>
</tr>
<tr>
<td>CAI, h/h</td>
<td>2±3 [0 to 15]</td>
</tr>
<tr>
<td>ODI, h/h</td>
<td>8±15 [0 to 61]</td>
</tr>
<tr>
<td>CT900, %</td>
<td>10±20 [0 to 95]</td>
</tr>
<tr>
<td>No. of antihypertensive drugs (% of patients)</td>
<td>1±1 [0 to 3] (61)</td>
</tr>
<tr>
<td>History of arterial hypertension (%)</td>
<td>26 (63)</td>
</tr>
<tr>
<td>Positive family history for vascular diseases</td>
<td>19 (46)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>8 (20)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>28 (68)</td>
</tr>
<tr>
<td>Hypercholesterinemia (%)</td>
<td>22 (54)</td>
</tr>
<tr>
<td>BMI &gt;25 (%)</td>
<td>25 (61)</td>
</tr>
<tr>
<td>Coronary heart disease (%)</td>
<td>8 (20)</td>
</tr>
</tbody>
</table>

Values are mean±SD (range in brackets) unless indicated otherwise.

Latency S-R indicates latency from stroke onset to respirography; CT900, percentage of time with oxygen saturation <90%.

Sleep Breathing
The mean AHI was 23±22/hour (0 to 101), AI was 11±16/hour (0 to 70), OAI was 2±3/hour (0 to 15), CAI was 8±15/hour (0 to 61), ODI was 14±15/hour (0 to 64), and percentage of time with oxygen saturation <90% was 10±20% (0 to 95). SA was found in 28 of 41 patients (68%). Eleven patients (27%) had a MSSA (mean AHI, 50±1/hour [31 to 101]; OAI, 5±5/hour [0 to 15]; and CAI, 24±23/hour [1 to 61]). Seventeen patients had a mild SA (mean AHI, 20±7/hour [10 to 29]; OAI, 3±3/hour [0 to 9]; and CAI, 6±7/hour [0 to 20]). In 13 patients (32%), no SA was found (mean AHI, 4±3/hour [0 to 8]; OAI, 1±1/hour [0 to 2]; and CAI, 1±1/hour [0 to 3]).

Considering the entire group of patients (n=41), a weak but statistically significant correlation between SA severity (AHI) and stroke severity on admission (NIHSS day 1 [r=0.33; P=0.035], SSS day 1 [r=−0.407; P=0.008]) and short-term outcome (mRS at discharge [r=0.341; P=0.031]) was observed. AHI remained significantly associated with both stroke severity (P=0.015) and stroke outcome (P=0.031) in a multiple stepwise linear regression model (Table 2).

When compared with patients without SA (n=13), patients with MSSA (n=11) had a higher BMI (P=0.001), a lower SSS on day 1 (P=0.046), and a longer duration of hospitalization (P=0.008). These and other results are shown in Table 3.
BP
History of arterial hypertension was present in 26 of 41 patients (63%). Twenty-five (61%) patients were treated with antihypertensive drugs. The mean BP during night 1 was 140±25 (100 to 239)/87±16 (63 to 147) mm Hg, during day 2 it was 153±24 (117 to 220)/97±15 (72 to 138) mm Hg, and during night 2 it was 144±31 (86 to 209)/90±20 (51 to 129) mm Hg. Patients with MSSA had higher systolic and diastolic BP values during night 1, day 2, and night 2 than patients without SA (Table 3; Figure).

Twenty-six patients (63%) were nondippers. Nondippers had more severe strokes (NIHSS day 1, AHI, OAI, mRS; F=10.89, P=0.001, R²=0.413; Full model for mRS; F=6.428, p=0.005, R²=0.300).

Conversely, there were no significant differences between dippers and nondippers regarding history of hypertension and respiratory parameters. A reverse dipping (BP night>BP day) was found in 7 patients (17%), 3 of whom had MSSA. These and other results are shown in Table 4.

Discussion
We investigated the evolution of BP in the acute stroke phase and its relationship to SA and stroke outcome. Our main results can be summarized as follows: (1) SA was found in 69% of patients, and its severity was associated with higher 24-hour BP values but only weakly with stroke severity and stroke outcome; and (2) a NDS was observed in 63% of patients and was linked to a more severe stroke and a worse stroke outcome but not with SA severity.

SA, BP, and Stroke Outcome
The high frequency of SA (69%) and MSSA (27%) in stroke victims is in line with previous reports.8–10 Our study also confirms the high proportion of hypopneas and central apneas in the first few nights after stroke (mean latency to sleep recording, 37±25 h),10 which contrasts with the predominance of obstructive and apneic events thereafter.9,30 The pathophysiological mechanisms involved therein remain unclear at this point.

In patients with SA, we found significantly higher systolic and diastolic BP values than in patients without SA. Furthermore, a linear, dose-response relationship between SA severity (AHI) and BP levels was observed, similar to what has been reported in the general SA population.3 These findings have, to our best knowledge, never been reported before in stroke victims. Turkington et al.24 found an increased BP variability (expressed as 10 and 15 mm Hg dips in BP) in 7 patients with SA (AHI>10/h), as compared with 5 patients without SA but did not provide data on absolute BP values.

Several mechanisms may explain higher BP values in stroke patients with SA including oscillations in cardiac output and heart rate, increased sympathetic activity, and impaired baroreceptor control.31,32 Considering the observation of a similar BP evolution in patients with and without SA, sleep disordered breathing appears to be a factor contributing to the overall poststroke increase of BP.

We observed only a weak relationship between SA severity and both stroke severity and short-term stroke outcome. Several previous studies also failed to find any significant link between...
stroke severity and SA.8–10,12 Data on SA and short-term stroke outcome are scarce and contradictory. In 1 study, worsening of neurological deficits in the acute phase was observed in patients with SA in the absence, however, of any detrimental effect on short-term stroke outcome.12 Conversely, Kaneko et al33 re-

Dippers (n=15) Nondippers (n=26) P

### TABLE 4. Comparison of Patients With and Without Nocturnal BP Dipping (See Text for Definition)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dippers</th>
<th>Nondippers</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female (%)</td>
<td>11/4 (73/27)</td>
<td>22/4 (85/15)</td>
<td>NS</td>
</tr>
<tr>
<td>Age, y</td>
<td>62±15</td>
<td>63±12</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28±4</td>
<td>27±3</td>
<td>NS</td>
</tr>
<tr>
<td>NIHSS day 1</td>
<td>5±3</td>
<td>9±5</td>
<td>0.004</td>
</tr>
<tr>
<td>SSS day 1</td>
<td>49±9</td>
<td>36±13</td>
<td>0.003</td>
</tr>
<tr>
<td>Latency S-R, h</td>
<td>45±24</td>
<td>32±24</td>
<td>NS</td>
</tr>
<tr>
<td>mRs at discharge</td>
<td>1.3±0.9</td>
<td>2.5±1.5</td>
<td>0.005</td>
</tr>
<tr>
<td>AHI, /h</td>
<td>21±14</td>
<td>24±25</td>
<td>NS</td>
</tr>
<tr>
<td>Ap, /h</td>
<td>10±12</td>
<td>11±18</td>
<td>NS</td>
</tr>
<tr>
<td>OA, /h</td>
<td>3±4</td>
<td>2±3</td>
<td>NS</td>
</tr>
<tr>
<td>CAI, /h</td>
<td>7±13</td>
<td>10±17</td>
<td>NS</td>
</tr>
<tr>
<td>ODI, /h</td>
<td>14±13</td>
<td>14±17</td>
<td>NS</td>
</tr>
<tr>
<td>CT90, %</td>
<td>11±26</td>
<td>9±14</td>
<td>NS</td>
</tr>
<tr>
<td>History of arterial hypertension (%)</td>
<td>12 (80)</td>
<td>14 (54)</td>
<td>NS</td>
</tr>
<tr>
<td>No. of antihypertensive drugs (%)</td>
<td>1.5±1.6 (87)</td>
<td>1.0±1.4 (42)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Systolic BP night 1, mm Hg: 127±20 148±25 0.011
Systolic BP day 2, mm Hg: 151±24 154±25 NS
Systolic BP night 2, mm Hg: 125±28 153±29 0.009
Diastolic BP night 1, mm Hg: 78±11 93±16 0.005
Diastolic BP day 2, mm Hg: 95±14 97±16 NS
Diastolic BP night 2, mm Hg: 78±17 96±19 0.009
Pulse night 1, beats/min: 59±6 68±13 0.011
Pulse day 2, beats/min: 67±7 73±13 NS
Pulse night 2, beats/min: 60±7 67±13 NS

NS indicates no significant difference; latency S-R, latency from stroke onset to respirography; CT90, percentage of time with oxygen saturation <90%.

Mean systolic and diastolic BP values during night 1, day 2, and night 2 in patients without SA (AHI<10/h), with mild SA (10/h<AH<30/h), and with MSSA (AHI>30/h). Values are mean±SD. SBP, systolic BP; DBP, diastolic BP. *P<0.05 compared with patients without SA (AHI<10/h).

Dipping Status, SA, and Stroke Outcome

We confirm that NDS, observed in 63% of patients, is a frequent phenomenon in acute ischemic stroke. This observation was made first by Sander and Klingelhofer.35 In a series of 86 patients with acute stroke, Lip et al18 found mean day-night differences in systolic and diastolic BP <10%, demonstrating that NDS was a common finding in this stage. Jain et al21 reported a NDS in 88% of 50 patients examined in the first 120 hours after stroke. In 58%, the mean nocturnal BP was even higher than daytime BP (reverse dipping).

Our data also suggest that loss of physiological nocturnal BP dipping is a stronger predictor for a worse stroke outcome than increased circadian BP values. Similar to us, Bhalla et al19 found that a decrease in day-night BP difference was associated with poor outcome in 72 patients 1 week after stroke. In hypertensive patients, Verdecchia et al16 reported that the number of combined fatal and nonfatal cardiovascular events per 100 patient-years was higher in patients with reduced nocturnal BP variation (4.99 in nondippers; 1.79 in dippers). Size and design of our study do not allow us to test the hypothesis of a link between stroke outcome and increased BP variability.24 BP values at both extremes of its spectrum,17 or hypotensive BP values after the first 24 hours.16

NDS is thought to arise from an imbalance between sympathetic and parasympathetic tone. This may be because of an
increased, stroke-related catecholamine and cortisol release, possibly reflecting the cerebral response to a decreased perfusion in the ischemic penumbra but also changes in the sleep-wake cycle and the acute stress of hospitalization. Based on our data, stroke severity and use of antihypertensive drugs at stroke onset, but not SA, influence the dipping status of acute stroke patients. Other studies have suggested a role also of stroke topography (cortical versus noncortical) and stroke etiology (hemorrhagic versus ischemic).18–21 Obviously, we cannot exclude, based on our data, the possibility that, in larger size studies including more patients, an association between NDS and SA of obstructive type could be found.

Conclusions

SA severity is associated with elevated circadian BP levels but only weakly with stroke severity and outcome. NDS predicts the presence of more severe stroke and poorer outcome but is not linked with SA severity. These data suggest that elevated circadian BP values and NDS have different, although overlapping, pathophysiological and clinical implications in acute ischemic stroke.

Acknowledgments

Prof Wilhelm Vetter, Department of Internal Medicine, University Hospital of Zurich, provided helpful comments on blood pressure results. Dr Esther Werth and Sabrina Döring, Department of Neurology, University Hospital of Zurich, assisted in the recording and scoring of polygraphies. We thank Dr Valentin Roussou for statistical advice.

References


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Stroke. 2005;36:2614-2618; originally published online November 10, 2005;
doi: 10.1161/01.STR.0000189689.65734.a3
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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