Changes of Circadian Blood Pressure Patterns After Hemodynamic and Thromboembolic Brain Infarction

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Background and Purpose  We investigated the changes of circadian blood pressure patterns after thromboembolic and hemodynamic brain infarction and evaluated the relation between circadian blood pressure variation, infarct location, and activation of the autonomic nervous system after thromboembolic stroke.

Methods  Repeated 24-hour blood pressure measurements were performed in 45 patients with proven first-ever brain infarctions of different origins. Evaluation of serum norepinephrine concentration, prolongation of the QT interval, and degree of cardiac arrhythmias were used to determine the extent of sympathetic activation after thromboembolic stroke.

Results  Whereas circadian blood pressure variation was significantly increased after hemodynamic infarction compared with a control group (diastolic, \(-25.2\pm4.5\%\) versus \(-13.8\pm6.5\%; P<.005\)), a clearly reduced variation was observed after thromboembolic stroke. Blood pressure variation was positively related to serum norepinephrine concentration (\(r=.79; P<.01\) after thromboembolic infarction). Patients with involvement of the insular cortex showed a nocturnal rise of blood pressure significantly more frequently (66.7\% versus 11.8\%; \(P<.005\)) and had higher norepinephrine levels (540±110 pg/mL versus 290±178 pg/mL; \(P<.01\)) than patients without insular cortex infarction, indicating increased sympathetic activity. This was associated with a significantly more frequent occurrence of QT prolongation and cardiac arrhythmias.

Conclusions  The observed differences in circadian blood pressure patterns may (1) help to distinguish the pathophysiological basis of the stroke, (2) help to explain worsening in some cases of hemodynamic stroke, (3) confirm the importance of the insular cortex for sympathetic activation, and (4) identify subgroups of patients with increased risk of myocardial infarction and arrhythmia. (Stroke. 1994;25:1730-1737.)

Key Words  • blood pressure • cerebral infarction • circadian rhythm • risk factors

Whereas the significance of hypertension as a primary risk factor for the development of cerebral infarction is well known, thus far only a few investigations have focused on the nature and extent of alterations of circadian blood pressure patterns after brain infarction. Cerebral infarctions of hemodynamic origin may occur when there is preexisting ipsilateral vascular disease with resulting focal cerebral hypoperfusion during episodes of systemic hypotension, eg, during the night.1,2 These "low-flow" infarcts are ischemic lesions that occur in the border zones between two major arterial territories or in the border zones between the superficial and deep territories of the middle cerebral artery.3,4

In contrast to this, thromboembolic territorial infarcts (depending on their extent and location) are frequently accompanied by an alteration of the autonomic nervous system.5,6 Thus, a pathological sympathetic activation is regarded as an important factor that might explain the increased incidence of cardiac arrhythmias and sudden cardiac death after cerebral infarction.7,8 Because the autonomic nervous system plays a major role in regulation of blood pressure, including diurnal and circadian

 alterations under physiological conditions,9 alterations of sympathoadrenergic activity can also affect the diurnal blood pressure profile. It has recently become possible to determine circadian blood pressure patterns with a noninvasive blood pressure monitoring system. Until now this method has mainly been used for more precise diagnostic appraisal and monitoring of antihypertensive therapy.10,11

The objective of our study was to analyze the changes of circadian blood pressure variation after cerebral infarctions of hemodynamic and thromboembolic origin and to establish their possible prognostic and therapeutic relevance. Furthermore, we investigated the relations between infarct location, activation of the autonomic nervous system, and changes of circadian blood pressure variation after thromboembolic cerebral infarction.

Subjects and Methods  From a series of 68 consecutive patients with a proven first-ever cerebral infarction of varying pathogenesis, 45 patients (mean age, 66±10.1 years; 17 women, 28 men) were included in this study. Ten patients showed a watershed infarction of hemodynamic origin, and 35 patients showed a hemispheric territorial infarction of thromboembolic origin. Only hospitalized patients with strictly unilateral brain infarcts and no other pathological findings on computed tomography (CT) or magnetic resonance imaging (MRI) were included. Potential patients were excluded from the study because (1) they received antiarrhythmic drugs (n=8) or agents known to influence the sympathetic nervous system (n=5); (2) the initial 24-hour blood pressure measurement after thromboembolic
infarction was not completed within the first 48 hours after stroke onset (n=6); or (3) they received antihypertensive medication during the 24-hour blood pressure measurements because of acute hypertensive values (n=4). Eighteen of the 35 patients (51.4%) had an infarct of the middle cerebral artery territory with involvement of the insular cortex, and 17 (48.6%) had an infarct sparing the insular cortex. Secondary hypertension was carefully ruled out in all patients. The age- and sex-matched control groups consisted of 30 normotensive hospitalized patients and 26 hospitalized patients with first-ever diagnosed primary arterial hypertension without prior cardiovascular events or antihypertensive medication. The classification was made in accordance with the results of the 24-hour blood pressure measurements. No patient of the control groups received antiarrhythmic drugs, antihypertensive medication, or agents known to influence the sympathetic nervous system during the 24-hour blood pressure measurements. To avoid a selection bias between control and infarction groups, only control patients with a level of activity similar to that of the stroke patients were evaluated.

The essential data of the four groups are shown in Table 1. The two infarction groups did not differ significantly with regard to age, sex, incidence of ischemic heart disease and diabetes mellitus, or severity of acute neurological deficit according to the Scandinavian Stroke Scale.13 In addition to Doppler ultrasonography of the extracranial and intracranial brain-supplying vessels, echocardiography and Holter electrocardiographic (ECG) monitoring were performed in all patients. In patients with hemodynamic infarction, vasomotor reactivity (VMR) was determined after CO2 stimulation.14 If Doppler ultrasonography showed a high-grade stenosis of a brain-supplying artery, digital arterial subtraction angiography was performed. According to Weiller et al,15 we defined an infarct as of hemodynamic origin when (1) a watershed infarction was detected on CT or MRI, (2) a high-grade stenosis or an occlusion of the internal carotid artery was found, or (3) a reduced VMR after CO2 stimulation was found.14 Moreover, there had to be no indications of a source of emboli on either echocardiography or Holter ECG monitoring.

The long-term blood pressure measurement (Spacelabs ABD-Monitor 90207) was repeatedly taken noninvasively by an oscillometric method during the clinical course. Validation studies that used this monitor demonstrated no significant differences of average systolic (~2%) and diastolic (+1%) blood pressure values compared with intra-arterial measurements.16-17 The measurements were made at intervals of 15 minutes during the entire 24-hour period. The average diurnal values were determined between 6 AM and 10 PM and the average nocturnal values between 10 PM and 6 AM. Circadian blood pressure variation was defined as the average percent change of blood pressure values at night compared with the day values. On average, 78±16 successful measurements were performed per patient during the 24-hour period. All measurements marked with an error event code on the monitor because of movement artifacts were manually dropped from the calculations. Systolic, diastolic, and mean blood pressures were reported. Hypertension was diagnosed when the average diurnal values were in excess of 135/85 mm Hg in the initial long-term blood pressure measurement.10,12 The initial measurement was completed in patients with territorial infarction within the first 48 hours after stroke onset and in patients with hemodynamic infarction within 1 week after the beginning of infarction (mean, 4±1.2 days; n=6) or during the phase of maximum contrast enhancement on CT or MRI (mean, 38±8 days; n=4). In all patients with thromboembolic infarction, a follow-up measurement was performed 7 to 10 days (mean, 8.6±0.7 days) after the beginning of infarction; additionally, in 11 of these patients (31.4%), follow-up measurements were performed for 21 or more days (mean, 27±6 days). Control measurements at monthly intervals at least 6 months after stroke onset were performed in all patients with hemodynamic infarction. The long-term measurement of blood pressure was made on the side ipsilateral to the infarct (unaffected arm) after relevant differences between the sides had been ruled out by conventional checks of blood pressure. The patients were instructed to keep their arms as quiet as possible during the measurement phase. Automatic artifact detection reduced possible measurement mistakes. The blood pressure monitor was manually calibrated for every patient before starting the
Results

Depending on the infarct type, clearly different blood pressure patterns could be demonstrated (Figs 1 and 2). After hemodynamic infarction (Fig 1, top panel), there was a substantially increased circadian blood pressure variation with hypertensive daily values (systolic, 151±16.1 mm Hg; diastolic, 91±10.1 mm Hg; upper normal average daily values during 24-hour blood pressure measurement, 135/85 mm Hg) and nocturnal hypotension (systolic, 118±12.7 mm Hg; diastolic, 66±11.0 mm Hg). Compared with the hypertensive and the normotensive control groups, the range of variation between the day and night values, with an average of 18.9±2.7% systolic and 25.2±4.5% diastolic, was significantly increased (P<.005 compared with the control groups; Fig 2, top panel) and was more than 40% in occasional cases. There was no significant difference of circadian blood pressure variation between patients with a measurement within 1 week compared with patients with a measurement during the phase of maximum contrast enhancement. In addition, there was a pronounced nocturnal hypotension, with minimum values down to 95/50 mm Hg in individual patients. In four patients with a high-grade stenosis (>90%) of the internal carotid artery, chronic arterial hypertension, and an additional inadequate collateralization capacity of the circle of Willis (VMR after CO2 stimulation, <40%), a prolonged disturbance of the blood-brain barrier was observed. The maximum contrast enhancement on both cerebral CT and MRI could be detected in these patients between day 34 and day 42 after the beginning of infarction. The blood pressure variation was clearly increased during this time (systolic, −20.0±2.15%; diastolic, −22.9±2.58%). In contrast to this, patients with territorial infarcts of thromboembolic origin (Fig 1, middle and bottom panels) showed a reduced circadian blood pressure variation in the initial phase (nocturnal reduction of systolic blood pressure, −4.2±6.0%, P<.005; diastolic, −5.2±6.9%, P<.001 compared with the control groups; Fig 2, top panel). The physiological nocturnal blood pressure decrease was no longer observed or was observed only to a limited extent even in patients who were initially normotensive. Only 11.4% of the patients showed a physiological reduction in nocturnal blood pressure (<−10%), and 48.6% did not show any significant lowering of the nocturnal blood pressure (−10% to 0%). Indeed, there was a nocturnal rise in blood pressure in 40% (Fig 2, bottom panel), which could be detected in only one patient (3.9%) in the hypertensive control group and in no patients in the normotensive control group (Fig 2, bottom panel; P<.001). The circadian blood pressure variation was comparable in the two control groups (Fig 2).

There was a significant linear correlation between serum norepinephrine concentration and circadian blood pressure variation (Fig 3, top panel). Accordingly, patients with thromboembolic infarction and a nocturnal rise in blood pressure showed on average significantly higher norepinephrine levels than thromboembolic stroke patients with maintained circadian blood pressure variation and a nocturnal fall in blood pressure (525±116 pg/mL, n=5 versus 337±204 pg/mL, n=7, respectively; P<.05). At the same time, 78.6% of the patients with a nocturnal blood pressure rise showed a QT interval prolongation, and 50%
showed an arrhythmia. In contrast to this, a QT prolongation could not be demonstrated in any patient with physiological nocturnal blood pressure reduction (<-10%; P<.01), and an arrhythmia was detected in only one patient (P<.05).

To analyze the effect of infarct location on circadian blood pressure changes, the patients with thromboembolic infarction were divided into subgroups with or without insular cortex infarction (Fig 1, Table 2). The age, sex, average potassium and calcium levels, average infarct size, incidence of diabetes mellitus or ischemic heart disease, and severity of acute neurological deficit according to the Scandinavian Stroke Scale were comparable between the two groups (Table 2). Compared with the normotensive and hypertensive control groups, there was a reduced circadian blood pressure variation in patients without insular cortex infarction, but on average a nocturnal reduction of blood pressure could be observed (Fig 1, middle panel). In contrast to this, there was on average a nocturnal rise in blood pressure in patients with involvement of the insular cortex (Table 2, bottom panel). In contrast to this, there was an increased rate of arrhythmia significantly more frequently (Table 2). Two of these patients (11.1%) but none of the other group developed myocardial infarction on days 5 and 7 after stroke.

In the subsequent clinical course, the patients with hemodynamic infarction did not show any appreciable change in the circadian blood pressure patterns without antihypertensive medication. In contrast to this, a significantly increased average circadian blood pressure variation was observed compared with the initial values (-8.5±4.8% versus -4.1±6.1%; P<.05) 7 to 10 days after stroke onset in the patients with thromboembolic infarction. However, this was still substantially less than the values of the hypertensive control group (P<.05). These findings were accompanied by a significant reduction of the norepinephrine concentration compared with the initial investigation (246±114 pg/mL versus 415±193 pg/mL; P<.01). Altogether, there was still a nocturnal rise of blood pressure in 11.4% of the patients with thromboembolic infarction, while only 31.4% showed a physiological nocturnal reduction of blood pressure (<-10%). Whereas no patient without involvement of the insular cortex showed a nocturnal rise of blood pressure, 33.3% of the patients with insular cortex infarction showed such a blood pressure pattern. In the third measurement after 21 days or more, no appreciable alteration of the blood pressure variation compared with the second investigation was observed.
Discussion

We found different changes of circadian blood pressure patterns after brain infarction depending on the pathogenesis and location of the stroke. In contrast to normotensive patients or patients with primary hypertension who showed a biphase circadian blood pressure pattern with physiological nocturnal blood pressure decreases in excess of 10%, there was a pathologically reduced or indeed abolished circadian blood pressure variation after thromboembolic hemispheric infarction. Initially, only a slight nocturnal reduction of blood pressure (~10% to 0%) was observed in 48.6% of the patients, and 40% showed a nocturnal rise of blood pressure. This indicates that an acute brain infarction led to a disturbance of the physiological biphase blood pressure regulation.

One could argue that the changes of blood pressure patterns are only due to differences in the level of activity or other unspecific factors. However, there were no significant differences in most clinical data and in the level of activity between patients with thromboembolic infarction and control subjects. The circadian blood pressure values of both control groups are comparable to recent findings in a large group of normotensive subjects as well as patients with primary hypertension and thus make it unlikely that there was a systematic selection bias concerning our control patients. Moreover, all patients were carefully screened to rule out secondary hypertension, in which an abolished circadian blood pressure pattern with nocturnal blood pressure increases could be observed. Furthermore, the pronounced effect of insular infarction on blood pressure patterns, cardiac parameters, and norepinephrine concentration indicates, in our opinion, that the observed changes could be ascribed to infarction itself rather than to unspecific effects.

Previous clinical investigations and experimental models of ischemic stroke elicited increased sympathetic activity after stroke, as suggested by raised plasma catecholamine levels, elevated serum cardiac enzyme values, increased sympathetic nerve activity, and increased incidence of arrhythmias and myocardial injury. In our investigation the patients with abolished circadian blood pressure rhythmicity showed a significantly higher norepinephrine concentration than the patients with maintained nocturnal reduction of blood pressure. The plasma norepinephrine concentration has been accepted as an index of peripheral...
sympathetic activity in previous studies. Moreover, various investigations demonstrated that the sympathetic system plays a major role in circadian blood pressure regulation. The diurnal fluctuations in blood pressure thus parallel the circadian catecholamine concentrations with a pronounced synchrony between the two parameters over 24 hours. The initial changes of the blood pressure patterns could thus be interpreted as a manifestation of increased sympathetic activity after thromboembolic stroke. This view was further supported by the fact that the normalization of blood pressure patterns during the follow-up was associated by a decrease of the initially elevated norepinephrine levels.

Several investigations indicate that the insular cortex is involved in the regulation of the autonomic nervous system. The importance of the insula in the mediation of the sympatheti- c consequences of stroke was first suggested by the results of experimental studies that demonstrated that in- farction of the insula is associated with raised plasma norepinephrine, increased sympathetic nerve activity, and myocardial damage. Recently, Oppenheimer et al demonstrated changes of cardiovascular parameters for the first time during intraoperative insular cortex stimulation in humans. Different alterations of blood pressure variation, plasma norepinephrine concentration, and ECG parameters depending on the location of the infarction were also demonstrated in our study, to our knowledge for the first time in humans. The patients with insular cortex infarction initially showed a significantly higher norepinephrine level, which correlated with a reduced or even absent circadian blood pressure variation and a nocturnal rise of blood pressure. As a sign of cardiac instability and increased sympathetic activity, these patients showed a QTc interval prolongation and an increased rate of arrhythmia during Holter ECG monitoring significantly more frequently than patients without insular cortex infarction. Because there are no major differences between these two groups for serum electrolytes, level of activity, incidence of ischemic heart disease or diabetes mellitus, and other clinical data, it is assumed that these clearly different ECG findings are related to the stroke. Our results indicate (although not always directly) that the insular cortex is involved in mediating the sympathetic consequences of stroke in humans and that insular cortex infarction leads to a pronounced pathologial sympathetic activation. These findings are also corroborated by the fact that two of the patients with insular cortex infarction (11.1%) developed myocardial infarction.

Since the likelihood of sudden death is not related to the cardiac status or the severity of stroke, it becomes difficult to monitor these patients. Our results indicate that analysis of circadian blood pressure patterns may be an additional useful parameter to appraise the extent of sympathetic activity and thus the danger to the patient. It seems clinically important that an abolition of circadian blood pressure variation was found in 11.4% of our patients 7 to 10 days after infarction and was detected almost unchanged after 3 weeks or more, whereas such a blood pressure pattern was not present in any normotensive patient and was present in only one hypertensive patient of the control groups. Indeed, 33.3% of the patients with insular cortex infarction continued to show a nocturnal rise of blood pressure, which indicates that an increased sympathetic activity persists for a long time in these patients. This may

### TABLE 2. Comparison Between the Two Thromboembolic Infarct Groups With and Without Insular Cortex Infarction

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Insular Infarction</th>
<th>No Insular Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67±11.4</td>
<td>65±10.0§</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>10/8</td>
<td>12/5§</td>
</tr>
<tr>
<td>SSS score</td>
<td>39±9</td>
<td>37±12§</td>
</tr>
<tr>
<td>Blood pressure,* mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>134±15</td>
<td>138±16§</td>
</tr>
<tr>
<td>Diastolic</td>
<td>78±9</td>
<td>83±12§</td>
</tr>
<tr>
<td>Side of infarction (right/left)</td>
<td>6/9</td>
<td>9/11§</td>
</tr>
<tr>
<td>Infarct volume, cm³</td>
<td>89±79</td>
<td>93±71§</td>
</tr>
<tr>
<td>Blood pressure variation, %†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase (&gt;0%), % of patients</td>
<td>66.7</td>
<td>11.8#</td>
</tr>
<tr>
<td>Decrease (&lt;−10%), % of patients</td>
<td>0</td>
<td>2.5%</td>
</tr>
<tr>
<td>Serum norepinephrine, pg/mL‡</td>
<td>540±110 (n=6)</td>
<td>290±178 (n=6)§</td>
</tr>
<tr>
<td>QTc prolongation, % of patients</td>
<td>66.7</td>
<td>17.7</td>
</tr>
<tr>
<td>Arrhythmia, % of patients</td>
<td>55.6</td>
<td>23.5</td>
</tr>
</tbody>
</table>

SSS Indicates Scandinavian Stroke Scale. Values are mean±SD where indicated.

*Initial average daily blood pressure values in the first 24-hour blood pressure measurement.
†Average percent change of mean blood pressure values at night compared with day values.
‡Initial values on the day of the first 24-hour blood pressure measurement.
explain the finding that an increased risk of sudden cardiac death is present for up to 30 days after stroke irrespective of the clinical state.29

In contrast to thromboembolic stroke, we found a pathologically increased circadian blood pressure variation after hemodynamic infarction. Whereas hypertensive blood pressure values were present without exception during the day, there was a pronounced reduction of the blood pressure values at night. This circadian blood pressure pattern differed conspicuously from the results in primary hypertension, in which there is usually an equivalent shift from day and night values to higher blood pressure values.10,12 Several studies suggest that low-flow infarctions may be related to the distinct hemodynamic effects of severe extracranial occlusive disease, with resulting cerebral hyperfusion during episodes of systemic hypotension.1,2 Nevertheless, it has been proposed that additional factors must be involved in the decrease in perfusion pressure that cause the low-flow infarct. Several authors have found a clearly reduced vasoconstriction reserve capacity or perfusion reserve, indicating an inadequate intracranial collateral blood supply after hemodynamic infarction with chronic hemodynamic compromise.14,16 In addition, the patients had only inadequately treated arterial hypertension. In chronic arterial hypertension, the autoregulation curve is shifted to higher blood pressure levels, leaving the brain less tolerant to acute cerebrovascular ischemia. In this situation, a decrease of blood pressure at night evidently led to a critical reduction of cerebral blood flow. Moreover, this mechanism may have led to the prolonged blood-brain barrier breakdown in four of our patients with chronic arterial hypertension and the most reduced VMR (<40%) as a morphological correlate of repeated nocturnal ischemia.

The identification of a subgroup of stroke patients with critically impaired cerebral hemodynamics may have a major impact on their management.1 To assert rapid and effective diagnostic and therapeutic strategies, low-flow infarctions must be differentiated from other subcortical stroke types such as lacunar infarction and large striatocapsular infarction. Llacunes are normally located in the basal ganglia and internal capsule, but such lesions may have the same size and site as low-flow infarcts. For differentiation, the evaluation of pathophysiological methods such as cerebral hemodynamic reserve has been proposed.13 Moreover, analysis of circadian blood pressure changes may provide useful additional information in patients with severe hemodynamic compromise: the constellation of an increased circadian blood pressure variation with hypertensive daily blood pressure values and nocturnal hypotension may indicate hemodynamic rather than thromboembolic mechanisms in these patients. In conclusion, the observed differences in circadian blood pressure patterns may (1) help to distinguish the pathophysiological basis of the stroke, (2) help to explain worsening in some cases of hemodynamic stroke, (3) confirm the importance of the insular cortex for sympathetic activation after brain infarction, and (4) identify subgroups of patients at increased risk for myocardial infarction and arrhythmia.

References


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Stroke. 1994;25:1730-1737
doi: 10.1161/01.STR.25.9.1730
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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