High NIHSS Values Predict Impairment of Cardiovascular Autonomic Control

Max Josef Hilz, MD; Sebastian Moeller, MD; Aynur Akhundova, MD; Harald Marthol, MD; Elisabeth Pauli, PhD; Philipp De Fina, MD; Stefan Schwab, MD

Background and Purpose—Stroke is frequently associated with autonomic dysfunction, which causes secondary cardiovascular complications. Early diagnosis of autonomic imbalance prevents complications, but it is only available at specialized centers. Widely available surrogate markers are needed. This study tested whether stroke severity, as assessed by National Institutes of Health Stroke Scale (NIHSS) scores, correlates with autonomic dysfunction and thus predicts risk of autonomic complications.

Methods—In 50 ischemic stroke patients, we assessed NIHSS scores and parameters of autonomic cardiovascular modulation within 24 hours after stroke onset and compared data with that of 32 healthy controls. We correlated NIHSS scores with parameters of total autonomic modulation (total powers of R-R interval [RRI] modulation; RRI standard deviation [RRI-SD], RRI coefficient of variation), parasympathetic modulation (square root of the mean squared differences of successive RRIs, RRI-high-frequency-powers), sympathetic modulation (normalized RRI-low-frequency-powers, blood pressure-low-frequency-powers), the index of sympatho-vagal balance (RRI-LF/HF-ratios), and baroreflex sensitivity.

Results—Patients had significantly higher blood pressure and respiration, but lower RRIs, RRI-SDs, RRI coefficient of variation, square root of the mean squared differences of successive RRIs, RRI-low-frequency-powers, RRI-high-frequency-powers, RRI-total powers, and baroreflex sensitivity than did controls. NIHSS scores correlated significantly with normalized RRI-low-frequency-powers and RRI-LF/HF-ratios, and indirectly with RRIs, RRI-SDs, square root of the mean squared differences of successive RRIs, RRI-high-frequency-powers, normalized RRI-high-frequency-powers, RRI-total-powers, and baroreflex sensitivity. Spearman-Rho values ranged from 0.29 to 0.47.

Conclusions—Increasing stroke severity was associated with progressive loss of overall autonomic modulation, decline in parasympathetic tone, and baroreflex sensitivity, as well as progressive shift toward sympathetic dominance. All autonomic changes put patients with more severe stroke at increasing risk of cardiovascular complications and poor outcome. NIHSS scores are suited to predict risk of autonomic dysregulation and can be used as premonitory signs of autonomic failure. (Stroke. 2011;42:1528-1533.)

Key Words: acute stroke ▪ autonomic imbalance ▪ NIHSS ▪ poststroke prognosis

Autonomic cardiovascular dysfunction is common after stroke.1–8 Sympathetic hyperactivity and parasympathetic dysfunction9 may cause tachy- or bradyarrhythmias,6,7 troponin T increase,10 myocardial infarction, or sudden death11,12 depending on brain area affected by the stroke.8,12,13

Altered or reduced heart rate variability during acute stroke may be prognostically unfavorable.9,14,15 Sykora et al16 showed reduced baroreflex sensitivity (BRS), ie, compromised autonomic adjustment of heart rate and vascular tone to sudden blood pressure (BP) changes, in acute and subacute stroke patients.5,17 They concluded that sympathetic overactivity and blunted BRS predict poor prognosis after stroke.5,15,18 Thus, early diagnosis of autonomic dysregulation has prognostic and therapeutic relevance in acute stroke.5,18

However, diagnosis of impaired autonomic BP and heart rate modulation requires specific techniques and expertise that is not widely available. Therefore, easily determined clinical surrogate markers of autonomic failure are desirable.

Based on previously reported correlations between autonomic impairment and clinical deficits,4,19 we hypothesize that readily available clinical stroke scale scores may serve as a surrogate measure of increased autonomic risk in acute stroke.

To determine whether acute clinical deficits reflect risk of autonomic cardiovascular dysregulation, we studied correla-
tions between parameters of autonomic modulation and the National Institutes of Health Stroke Scale (NIHSS) scores in acute stroke patients.

### Patients and Methods

In 50 patients (25 women, 25 men; age 48–84 years; mean age, 66±13 years) with acute, first-ever ischemic stroke in the middle cerebral artery territory (28 left-hemispheric and 22 right-hemispheric strokes), we assessed clinical stroke severity by means of NIHSS (range, 0–42 points); we also monitored cardiovascular autonomic modulation within 50 minutes to 23 hours (mean, 589±444 minutes) after stroke onset. Patients with other diseases and medication that affect the autonomic nervous system were excluded from the study. Patient data were compared with those of 32 age-matched healthy controls (20 women, 12 men; mean age, 61±8 years). We recruited healthy volunteers among unaffected relatives and friends of patients and among members of our research team. The study was approved by the ethics committee of the University of Erlangen-Nuremberg.

To derive parameters of cardiovascular autonomic modulation, we recorded 5-minute time-series of R-R-interval (RRI), BP, respiratory frequency, and transcutaneous oxygen saturation (SatO2). RRIs were recorded by conventional 3-lead electrocardiography. Beat-to-beat systolic and diastolic blood pressures (BPsys, BPdia) were measured noninvasively at the index or middle finger of the nonparetic hand, using the vascular unloading technique (CNAP™, Dräger Medical), then were calibrated against ipsilateral brachial artery BP. Respiration frequency was recorded by chest impedance measurements. SatO2 was measured by pulse-oximetry (Draeger Medical). Respiratory frequency was recorded by conventional 3-lead electrocardiography. Beat-to-beat systolic and diastolic blood pressures (BPsys, BPdia) were measured noninvasively at the index or middle finger of the nonparetic hand, using the vascular unloading technique (CNAP™, Dräger Medical), then were calibrated against ipsilateral brachial artery BP. Respiratory frequency was recorded by chest impedance measurements. SatO2 was measured by pulse-oximetry (Draeger Medical).

All signals were sampled at 200 Hz, digitized, and stored for data analysis on a custom-designed data acquisition and analysis system (SUEmpathy™, SUESS Medizin-Technik).

From 5-minute recordings without artifacts, we extracted the most stationary 90-second periods of all signals. To avoid a bias regarding the signal epoch selected for data analysis, we extracted the most stationary 90-second period from the 5-minute recordings while blinded to the participant’s status (eg, sex, age, healthy control or patient, NIHSS score).

As autonomic parameters, we determined the coefficient of variation of RRIs (RRI-CV), RRI-CV and RRI-SD reflect sympathetic and parasympathetic cardiac modulation.23,24 We calculated square root of the mean squared differences of successive RRIs (RMSSD), reflecting parasympathetic cardiac modulation.23,24

We performed trigonometric regressive spectral analyses22 of slow, underlying RRI and BP oscillations in frequency ranges reflecting sympathetic and parasympathetic influences on RRI and BP.25

We identified peaks of oscillations in the so-called low-frequency (LF; 0.04–0.14 Hz) and high-frequency (HF; 0.15–0.50 Hz) ranges of RRI and BP modulation.23,24

LF oscillations of RRI at rest are considered to be mediated by sympathetic outflow and, to an undetermined degree, also by parasympathetic activity; meanwhile, LF oscillations of BP are related to sympathetic outflow only.23,24 HF oscillations in RRI reflect parasympathetic activity,23,24 whereas BP fluctuations in the HF range are primarily a mechanical consequence of respiration-induced fluctuations in venous return and cardiac output.23,24

The magnitude of LF and HF oscillations was determined as the integral under the power spectral density curves of RRI (ms²/Hz) and BP (mm Hg²/Hz) for the 2 frequency bands, and was expressed as LF- and HF-powers of RRI (ms²) and BP (mm Hg²).25

In addition, we calculated RRI-LF/HF-ratios as an index of sympatho-vagal balance, and the sum of LF- and HF-powers as an approximation of the total power of RRI oscillations and index of overall autonomic cardiac modulation.23,24 We normalized RRI-LF- and RRI-HF-powers to reduce effects of interindividual differences in total powers on absolute RRI-LF- and RRI-HF-powers,26 where RRI-LFnu=(RRI-LF/[RRI-LF+RRI-HF])×100%, and RRI-HFnu=(RRI-HF/[RRI-LF+RRI-HF])×100%.23,24 To determine BRS, the trigonometric regressive spectral software selected pairs of LF and HF oscillations of BPsys, and RRI with high coherence values of the recorded bio-signals and with parameters of autonomic modulation were compared using the nonparametric Mann-Whitney-test.

†Significant differences between patients and controls.
‡P-values derived from 1-tailed tests.
*P-values derived from the nonparametric Mann-Whitney-test.

### Statistics

For data analysis, we used a commercially available statistical program (SPSS 18.0, SPSS Inc.). We tested data for normal distribution by the Shapiro-Wilk test.

Normally distributed patient and control data were compared using the t test for unpaired samples. Non-normally distributed data were compared using the Mann-Whitney U test.

Correlations between NIHSS scores and bio-signals as well as autonomic parameters and BRS were assessed with the Spearman rank correlation test.

Using the Spearman rank correlation test, we also calculated correlations between the interval from stroke onset to autonomic testing and the NIHSS scores, and we correlated the interval with values of the recorded bio-signals and with parameters of autonomic modulation. Significance was assumed for P<0.05.

### Results

In 50 stroke patients, NIHSS scores ranged from 1 to 21 (median, 5; lower quartile, 3; upper quartile, 11). Table 1 summarizes data of patients and controls.

In patients, BPsys and respiratory frequency were significantly higher than they were in controls, whereas RRIs, RRI-SD, RRI-CV, and RMSSD were lower in patients than they were in controls (Table 1).

### Table 1. Mean Values and SD of 50 Patients With Acute, First-Ever Ischemic Stroke in the MCA-Territory and 32 Age-Matched Controls

<table>
<thead>
<tr>
<th>Parameter, Mean ± SD</th>
<th>MCA Stroke (n=50)</th>
<th>Control (n=32)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>65.8±12.7</td>
<td>61.9±7.6</td>
<td>0.085*</td>
</tr>
<tr>
<td>RRI, ms</td>
<td>779.1±141.2†</td>
<td>937.6±117.5†</td>
<td>0.000†</td>
</tr>
<tr>
<td>RRI-SD, ms</td>
<td>17.3±8.2†</td>
<td>24.4±8.3†</td>
<td>0.000†</td>
</tr>
<tr>
<td>RRI-CV, %</td>
<td>2.2±1.0†</td>
<td>2.6±0.9†</td>
<td>0.021†*</td>
</tr>
<tr>
<td>RMSSD, ms</td>
<td>15.1±8.7†</td>
<td>19.2±9.5†</td>
<td>0.023†*</td>
</tr>
<tr>
<td>BPsys, mm Hg</td>
<td>143.3±27.4†</td>
<td>132.2±18.6†</td>
<td>0.048†</td>
</tr>
<tr>
<td>BPdia, mm Hg</td>
<td>78.9±18.3</td>
<td>72.6±10.7</td>
<td>0.079†</td>
</tr>
<tr>
<td>Respiratory frequency, min⁻¹</td>
<td>17.0±3.5†</td>
<td>13.6±4.7†</td>
<td>0.000†</td>
</tr>
<tr>
<td>RRI-LF-powers, ms²</td>
<td>182.2±211.8†</td>
<td>296.8±208.4†</td>
<td>0.000†</td>
</tr>
<tr>
<td>RRI-LFnu-powers, %</td>
<td>68.5±19.7</td>
<td>70.0±13.5</td>
<td>0.716‡</td>
</tr>
<tr>
<td>RRI-HF-powers, ms²</td>
<td>69.2±61.5†</td>
<td>124.1±122.3†</td>
<td>0.005†</td>
</tr>
<tr>
<td>RRI-HFnu-powers, %</td>
<td>31.5±19.7</td>
<td>30.0±13.5</td>
<td>0.716‡</td>
</tr>
<tr>
<td>RRI-total powers, ms²</td>
<td>251.2±232.7†</td>
<td>421.0±277.8†</td>
<td>0.001†</td>
</tr>
<tr>
<td>RRI-LF/HF-ratios</td>
<td>5.0±6.5</td>
<td>3.5±3.3</td>
<td>0.909*</td>
</tr>
<tr>
<td>BPsys-LF-powers, mm Hg</td>
<td>8.2±7.6</td>
<td>7.7±7.0</td>
<td>0.879*</td>
</tr>
<tr>
<td>BPsys-HF-powers, mm Hg</td>
<td>3.0±6.1</td>
<td>1.6±1.9</td>
<td>0.463*</td>
</tr>
<tr>
<td>BRS, ms-mm Hg⁻¹</td>
<td>5.3±2.8†</td>
<td>7.0±3.7†</td>
<td>0.023†</td>
</tr>
</tbody>
</table>

RRI, R-R interval; RRI-SD, SD of RRIs; RRI-CV, coefficient of variation of RRIs; RMSSD, square root of the mean squared differences of successive RRIs; BPsys, systolic blood pressure; BPdia, diastolic BP; LF, low frequency; HF, high frequency; nu, normalized units; RRI-LF/HF-ratios, low-frequency/high-frequency-ratios of RRIs; BRS, baroreflex sensitivity.

*P-values derived from the nonparametric Mann-Whitney-test.
†Significant differences between patients and controls.
‡P-values derived from 1-tailed tests.

In stroke patients, BRS was lower in patients than it was in controls (Table 1).
Similarly, patients had lower RRI-LF-powers, RRI-HF-powers, RRI-total powers, and BRS than did controls (Table 1). BPdia values were not quite significantly higher in patients than in controls ($P=0.07$), while BPsys-LF-powers, BPsys-HF-powers, normalized RRI-LF-powers, normalized RRI-HF-powers, and RRI-LF/HF-ratios did not differ between patients and controls ($P>0.05$).

NIHSS scores correlated significantly with normalized RRI-LF-powers and RRI-LF/HF-ratios, while there were an inverse correlations between NIHSS scores and RRI-SDs, RMSSD, RRI-HF-powers, normalized RRI-HF-powers, RRI-total powers, and BRS (for Spearman-Rho-values, see Table 2).

There were no significant correlations between NIHSS scores and BP$_{sys}$, BP$_{dia}$, SatO$_2$, respiratory frequency, RRI-CV, absolute RRI-LF-powers, and BP$_{sys}$-LF-powers.

There was no significant correlation between NIHSS scores and the interval from stroke onset to autonomic testing (Spearman Rho, 0.218; $P=0.128$).

Moreover, there were no significant correlations between this interval and RRI-SDs, BP$_{sys}$, BP$_{dia}$, respiratory frequency, SatO$_2$, RRI-CVs, RRI-LF-powers, RRI-LF/HF-ratios, normalized RRI-LF- and RRI-HF-powers, BP$_{sys}$-LF-powers, BP$_{sys}$-HF-powers, and BRS. In contrast, the interval correlated with the parasympathetic indices RMSSD of RRI ($Rho=0.308$; $P=0.029$), RRI-HF-powers ($Rho=0.415$; $P=0.003$), and with the index of overall autonomic cardiac modulation, the sum of RRI-LF-powers and RRI-HF-powers (RRI-total powers; $Rho=0.284$; $P=0.046$).

### Discussion

Our stroke patients had higher BP, heart rate, and respiratory frequency than did controls, indicating increased sympathetic cardiovascular modulation.6-7,9,28-30 However, the lower RRI-LF-powers, lower sympathetically and parasympathetically mediated RRI-SDs, RRI-CVs, and RRI-total powers23,24 in patients than in controls show a general loss of autonomic cardiac modulation; this has been reported in previous stroke studies.6,7,28 In contrast to the increase in BP, heart rate, and respiratory frequency of our patients, similar RRI-LF/HF-ratios between patients and controls seem to suggest that there is no major change in sympatho-vagal balance after stroke. Yet, increasing RRI-LF/HF-ratios in patients with higher NIHSS scores, as well as the lower RMSSDs and RRI-HF-powers in patients than in controls, confirm a loss in parasympathetic modulation after stroke, and predominant sympathetic tone with increasing stroke severity.

Previous studies support the conclusion that autonomic imbalance depends on stroke severity. Korpelainen et al4 report no increase in RRI-LF/HF-ratios in patients with higher NIHSS scores, as well as the lower RMSSDs and RRI-HF-powers in patients than in controls, confirm a loss in parasympathetic modulation after stroke, and predominant sympathetic tone with increasing stroke severity.

### Table 2. Spearman Rho Values of Correlations in 50 Patients With Acute, First-Ever Ischemic Stroke in the MCA Territory

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Spearman Rho</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRI, ms</td>
<td>-0.310</td>
<td>0.028</td>
</tr>
<tr>
<td>RRI-SD, ms</td>
<td>-0.289</td>
<td>0.042</td>
</tr>
<tr>
<td>RRI-CV, %</td>
<td>-0.218</td>
<td>0.129</td>
</tr>
<tr>
<td>RMSSD, ms</td>
<td>-0.421</td>
<td>0.002</td>
</tr>
<tr>
<td>BP$_{sys}$, mm Hg</td>
<td>-0.092</td>
<td>0.526</td>
</tr>
<tr>
<td>BP$_{dia}$, mm Hg</td>
<td>-0.101</td>
<td>0.487</td>
</tr>
<tr>
<td>Respiratory frequency, min$^{-1}$</td>
<td>-0.068</td>
<td>0.641</td>
</tr>
<tr>
<td>O$_2$-saturation, %</td>
<td>0.067</td>
<td>0.642</td>
</tr>
<tr>
<td>RRI-LF-powers, ms$^2$</td>
<td>0.177</td>
<td>0.219</td>
</tr>
<tr>
<td>RRI-LFnu-powers, %</td>
<td>0.345</td>
<td>0.014</td>
</tr>
<tr>
<td>RRI-HF-powers, ms$^2$</td>
<td>-0.466</td>
<td>0.001</td>
</tr>
<tr>
<td>RRI-HFnu-powers, %</td>
<td>-0.345</td>
<td>0.014</td>
</tr>
<tr>
<td>RRI-total powers, ms$^2$</td>
<td>-0.292</td>
<td>0.039</td>
</tr>
<tr>
<td>RRI-LF/HF-ratios</td>
<td>0.345</td>
<td>0.014</td>
</tr>
<tr>
<td>BP$_{sys}$-LF-powers, mm Hg$^2$</td>
<td>-0.032</td>
<td>0.828</td>
</tr>
<tr>
<td>BP$_{sys}$HF-powers, mm Hg$^2$</td>
<td>0.125</td>
<td>0.386</td>
</tr>
<tr>
<td>BRS, ms-mm Hg$^{-1}$</td>
<td>-0.317</td>
<td>0.025</td>
</tr>
</tbody>
</table>

RRI, R-R intervals; RRI-SD, standard deviation of RRI; RRI-CV, coefficient of variation of RRI; RMSSD, square root of the mean squared differences of successive RRIs; BP$_{sys}$, systolic blood pressure; BP$_{dia}$, diastolic BP; LF, low frequency; HF, high frequency; nu, normalized units; RRI-LF/HF-ratio, low-frequency/high-frequency-ratio of RRIs; BRS, baroreflex sensitivity.

![Figure. Correlations between individual NIHSS score values and A: RR-intervals (RRIs), B: normalized RRI-LF-powers, C: normalized RRI-HF-powers.](http://stroke.ahajournals.org/Download_articles/1530_Stroke_June_2011.pdf)
The correlations seen in our patients between NIHSS scores and parameters of autonomic modulation (Figure) indicate a higher risk of autonomic complications in patients with more severe strokes. Tokgözoglu et al observed an association between sudden death and reduced parasympathetic, but increased sympathetic activity in their 62 stroke patients.6 The 7 patients who died unexpectedly during hospitalization had higher RRI-LF/HF-ratios than did surviving patients.8 Among 44 stroke patients, Orlandi et al found increased RRI-LF/HF-ratios in the 31 patients with arrhythmias.7

Sympathetic predominance increases the risk of poststroke tachyarrhythmias,6,7 myocardial infarctions,10,12 myofibrillar necrosis, perivascular and interstitial fibrosis, and myocyte vacuolization10,32; it additionally increases the risk of secondary brain injury and edema caused by sympathetically driven inflammation with fever, hyperglycemia, polycythemia, and increased blood-brain barrier permeability.18,33 Consequently, increased sympathetic outflow compromises stroke outcome.29

The progressive decline in parasympathetic activity in our patients with more severe strokes adds to the risk of cardiovascular and cerebral complications.34 Parasympathetic deficiency promotes malignant tachyarrhythmias8,13,34,35 and mortality,36 reduces cerebral vasodilatation in animal stroke studies, and subsequently furthers cerebral vasoconstriction37 and secondary brain damage.38

The overall loss in autonomic modulation, ie, the decreasing RRI-SDs and RRI-total powers in patients with higher NIHSS scores, is associated with a growing risk of cardiac complications and sudden death.14,39

Declining autonomic modulation predicts poor outcome, as shown in patients with myocardial infarction,40 chronic heart failure,41 multiple organ dysfunction syndrome,42 and in ischemic stroke.4,14

Progressive loss in autonomic modulation in patients with more severe stroke also causes deteriorating heart rate and BP adjustment to instantaneous changes of either parameter because of declining BRS.17 Sykora et al showed that BRS impairment depends on the volume of the stroke and involvement of the insula18; they confirm the conclusions of Robinson et al that BRS deterioration after stroke reflects central autonomic dysfunction.19 Similar to our results, Sykora et al found correlations between decreasing BRS and increasing NIHSS scores.19

Reduced BRS is associated with poor outcome in cardiac, renal, or metabolic diseases,40,43 and in stroke.5,15 According to Robinson et al, BRS impairment during acute stroke is associated with a 4.5-fold increase in mortality rates.15 Baroreflex failure results in increased BP fluctuations45 that may exceed cerebral autoregulation buffering capacity45; this causes secondary cerebral lesions,46 particularly in patients with more severe stroke and more deficient BRS. BP fluctuations worsen stroke outcome, as they cause more severe end-organ damage than does nonfluctuating arterial hypertension.47

In our patients, coefficients of correlation between increasing NIHSS scores and deteriorating autonomic parameters range from Spearman Rho values of 0.29 to 0.47. Still, the high consistency of correlations between stroke severity and all measures of autonomic dysregulation confirms that more severe stroke is associated with more pronounced autonomic failure and subsequent risk of secondary cardiovascular6,7,10,12,18,29,30 or cerebral complications.18,31,37,38

Study Limitations
The rather wide interval between stroke onset and autonomic testing, from 50 minutes to 23 hours, might bias our results. However, NIHSS scores were not dependent on the interval between stroke onset and autonomic evaluation. In contrast, there seems to be inconsistent correlations between this interval and some of the autonomic parameters. Particularly, the positive correlation of the interval between stroke onset and autonomic testing with the parasympathetic parameters RMSSD and RRI-HF-powers suggests that parasympathetic modulation recovers with increasing time since stroke onset. Moreover, the correlation of the interval with overall autonomic modulation points toward the potential for regaining autonomic control over time. The findings encourage follow-up assessments of autonomic control to determine the duration and time course of autonomic dysfunction.

Although we found significant correlations between NIHSS scores and parameters of cardiovascular autonomic dysfunction, there is substantial variability within these correlations. We assume that this variability is because of the effects of age and sex on autonomic parameters, and because of the difference between discontinuous NIHSS scoring and continuous values of autonomic function.

In contrast to continuous values of autonomic parameters, the NIHSS is designed as a straightforward scoring system that assigns noncontinuous scores to the major clinical deficiencies without reflecting the entire scope of deficits in an individual stroke patient (eg, apraxias and neurocognitive deficits).20,48 Consequently, stroke severity may be categorized by the same NIHSS score in patients with a different extent or location of the neurological lesion. In contrast, involvement of different parts of the central autonomic network most likely accounts for differences in autonomic dysfunction and thus different values of parameters reflecting dysautonomia.49

Moreover, most autonomic parameters vary with differences in age and sex50,51 while NIHSS scores are independent of the patient’s sex or age. The age range of our patients was rather wide (48 to 84 years) and very likely contributed to the variation in autonomic parameters, regardless of NIHSS scores. Similarly, differences in sex, with 25 male and 25 female stroke patients, contribute to the variation in autonomic parameters, again regardless of the NIHSS score.50,51

The variability of autonomic parameters demonstrates the need for refined autonomic testing in stroke patients. Yet, the methodology is not readily available. Despite the rather wide variability of autonomic parameters for a given NIHSS score, the consistency of correlations between the autonomic parameters and NIHSS scores still supports the conclusion that NIHSS scoring may serve as a coarse substitute for sophisticated autonomic assessment.

In summary and in conformity with previous studies,4,7,14,15,28 our results demonstrate the need for autonomic monitoring of
stroke patients to prevent complications caused by autonomic failure.

However, autonomic monitoring is not widely available; and, yet, NIHSS scores are easily taken. From the correlations seen in our patients, we suggest that NIHSS scores may serve as surrogate markers of progressive autonomic failure. Deteriorating NIHSS scores require close observation of heart rate, BP, and the variabilities of those measures. Loss of heart rate variability and increasing BP variability indicate growing autonomic risk and predict the need for interventions to stabilize the cardiovascular system.

Perspective
There are many reports about differences in autonomic dysfunction after left- and right-sided stroke.\textsuperscript{2,3,6,8,29,52} Although many studies found a shift toward more prominent sympathetic modulation after right-hemispheric stroke,\textsuperscript{5,11,29,52,53} there are also reports that only found a decrease in total autonomic modulation\textsuperscript{4} or a decrease in parasympathetic outflow after right-hemispheric stroke.\textsuperscript{2,54} Moreover, NIHSS scores are higher with left-sided than with right-sided stroke.\textsuperscript{4,55–59}

Therefore, we assume that the correlations seen between NIHSS scores and autonomic parameters might be hemisphere-dependent. Hemispheric predominance of autonomic modulation\textsuperscript{50} might account for discrepancies of autonomic dysfunction and of its correlation with NIHSS scores between patients with right and left middle cerebral artery stroke. A preliminary analysis of our hemisphere-specific data suggests there are quite complex and intricate interactions between the side of the lesion and the dysautonomia. Yet, it is beyond the scope of this article to present and discuss the hemisphere-specific data. We, however, intend to provide a separate detailed analysis of hemispheric correlations and differences.

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Disclosures
None.

References
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高い NIHSS 値は心血管系自律神経調節の障害を予測する

密Josef Hilz, MD1,2; Sebastian Moeller, MD3; Aynur Akhundova, MD1; Harald Marthol, MD1; Elisabeth Pauli, PhD1; Philipp De Fina, MD3; Stefan Schwab, MD1

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背景および目的: 脳卒中はしばしば自律神経機能障害を伴っており、これは続発性の心血管系合併症の原因となる。自律神経失調の早期診断により合併症は予防されるが、これらは専門の機関でのみ可能であり、広く利用可能な代替マーカーが必要である。本研究では、NIHSS スコアにより評価した脳卒中の重症度が自律神経機能障害と相関するかどうか、したがって自律神経合併症のリスクを予測するかどうかを検証した。

方法: 50 例の虚血性脳卒中患者を対象に、脳卒中の発症から 24 時間以内の NIHSS スコアおよび自律神経性心血管系調節のパラメータを評価し、データを 32 例の健康対照者と比較した。NIHSS スコアを、総合的自律神経調節 (R-R 間隔 [RRI] 調節の総周波成分; RRI 標準偏差 [RRI-SD], RRI 変動係数) , 副交感神経調節 (連続する RRI の平均二乗差の平方根,RRI-HF 成分) , 交感神経調節 (正規化した RRI-LF 成分, 血圧-LF 成分) , 交感神経 - 迷走神経バランスの指標 (RRI-LF/HF 比) および圧反射感受性のパラメータと相関させた。

結果: 患者は対照と比べて血圧および呼吸数は有意に高かったが、RRI, RRI-SD, RRI 変動係数、連続する RRI の平均二乗差の平方根, RRI-LF 成分, RRI-HF 成分, RRI- 総周波成分、および圧反射感受性は低かった。

NIHSS スコアは正規化した RRI-LF 成分および RRI-LF/HF 比と有意に相関し、RRI, RRI-SD, 連続する RRI の平均二乗差の平方根, RRI-HF 成分, 正規化した RRI-HF 成分, RRI- 総周波成分、および圧反射感受性と負の相関を示した。Spearman の ρ 値は 0.29 ～ 0.47 の範囲であった。

結論: 脳卒中の重症度の上昇は、全体的自律神経調節の進行性消失、副交感神経緊張と圧反射感受性の低下、ならびに交感神経優位への進行性移行を伴っていた。脳卒中の重症度が高い患者では、あらゆる自律神経系の変化に伴って心血管系合併症および転帰不良のリスクが上昇する。NIHSS スコアは自律神経失調のリスクの予測に適しており、自律神経不全の前駆徴候として使用できる可能性がある。

Stroke 2011; 42: 1528-1533

図: 個々の NIHSS スコア値と(A) RRI 間隔 (RRI), (B) 正規化した RRI-LF 成分, (C) 正規化した RRI-HF 成分との相関。

RRI-LF: 低周波 RRI, RRI-HF: 高周波 RRI.
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高 NIHSS 评分预测受损的心血管自主神经控制

Max Josef Hilz, MD; Sebastian Moeller, MD; Aynur Akhundova, MD; Harald Marthol, MD; Elisabeth Pauli, PhD; Philipp De Fina, MD; Stefan Schwab, MD

背景和目的：脑卒中与心血管自主神经紊乱密切相关，从而引起继发性的心血管并发症。对自主神经功能紊乱的早期诊断能够预防并发症的发生，但是只有专业的中心能够做到。我们需要能够广泛利用的替代指标。本研究就是通过评价 NIHSS 评分，从而确认卒中的严重性是否与自主神经功能紊乱相关，从而预测并发症的发病风险。

方法：对50名缺血性卒中患者，在发病24小时内进行 NIHSS 评分和心血管自主调节能力的参数进行评估，并与32名健康对照组进行数据比较。行 NIHSS 评分和总自主神经调节参数（总的 R-R 间隔 [RRI] 的调节；RRI 的标准差 [RRI-SD]；RRI 的变异系数）的偏相关分析；交感神经调节参数（正常化低频率，血压低频率），交感神经 - 迷走神经平衡指数（RRI-LF/HF 比率）以及压力感受器的敏感性的相关性分析。

结果：与对照组相比，患者有明显的较高血压及通气，但是 RRI、RRI-SDs、RRI 相关变量、连续 RRI 均方的平方根、RRI 低频率、RRI 高频率以及压力感受器的敏感性低。NIHSS 评分与正常的 RRI 低频率及 RRI-LF/HF 比率明显相关，间接与 RRI、RRI-SDs、RRI 相关变量、连续 RRI 均方的平方根、RRI 低频率、RRI 高频率以及压力感受器的敏感性相关。Spearman-Rho 值在 0.29-0.47 之间。

结论：逐渐增加的卒中严重性与进展性的总体自主神经调节丧失、交感神经敏感性和压力感受器敏感性下降，以及进展性转移至交感神经主导相关。所有的自主改变使较严重的卒中患者增加了心血管并发症的风险及不良预后。NIHSS 评分适合于预测自主失衡的风险，并且可以用来作为自主调节失衡的预兆。

关键词：急性卒中，自主神经失调，NIHSS，卒中预后

(Stroke. 2011;42:1528-1533. 北京天坛医院神经内科 吴建维 译 刘丽萍 校)
年龄 48-84；平均年龄 66±13 岁），均为首次发病的大脑中动脉供血区的急性缺血性卒中（28 例位于左侧大脑半球，22 例位于右侧大脑半球），我们使用 NIHSS 评分代表卒中的严重程度（0-42 分）；我们检测卒中发生 50 分钟至 23 小时（平均为 589±444 分钟）的心血管自主神经功能。合并能够影响自主神经系统的其他疾病或者药物的患者被排除。病人的数据与年龄匹配的 32 名健康的对照组（女性 20 名，男性 12 名，年龄 61-88 岁）进行比较。该实验被 Erlangen-Nuremberg 的伦理委员会所通过。

为了得到心血管自主调节的参数，我们记录了以 5 分钟为时间段的连续的 R-R 间期（RRI）、BP(收缩压 BPsys，而舒张压 BPdia) 通过使用血管舒张技术（CNAP™, Dräger Medical）的非偏瘫手的食指或中指测量，然后校准患侧肱动脉。呼吸频率，呼吸频率, 单位为呼吸每分钟 min^{−1}。我们辨识了所有的信号在 200 Hz 取样，数字化，并且储存在一个定制设计的数据采集以及分析系统 (SUEmpathy™, SUESS Medizin-Technik) 中分析 [23]。

从没有人工干预的 5 分钟中，我们取出最静止的 90 秒，然后计算所有信号的平均值和标准差。考虑到为避免数据分析的信号时间选择的偏倚，对患者基本状态 (如性别、年龄、健康对照或患者、NIHSS) 采用盲法，并选择 5 分钟记录中最静止的 90 秒。

作为自主神经参数，我们确定了 RRI 变异系数 (RRI-CV)。RRI-CV 及 RRI-SD 反映了交感神经及副交感神经的心脏调节 [23,24]。我们计算连续 RRI 的方差 (RMSSD)，其反应了副交感神经的心脏调节 [23,24]。

我们对慢的、潜在的 RRI 和 BP 振荡在频率范围内进行了三角函数退调分析 [23]，反应了交感神经和副交感神经的影响 RRI 和 BP [23]。

我们辨识了 RRI 和 BP 调节在所谓的低频 (LF，0.04-0.14 Hz) 和高频 (HF，0.15-0.50 Hz) 范围内的振荡高峰 [23,24]。

RRI 的低频振荡在休息时被认为是交感神经输出介导，并且在某种程度上，也受副交感神经的活性影响。同时，BP 的低频振荡也与交感神经的输出相联系 [23,24]。RRI 的高频振荡反应了副交感神经的活动 [23,24]，而 BP 的高频振荡主要是呼吸诱导的静脉回流以及心脏输出机制的影响 [23,24]。

通过脉冲血氧仪 RRI

表 1 50 名急性大脑中动脉区域的缺血性卒中患者及 30 名对照组的数据的均值及标准差

<table>
<thead>
<tr>
<th>参数</th>
<th>卒中患者 (n=50)</th>
<th>对照组 (n=32)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>年龄，岁</td>
<td>65.8±12.7</td>
<td>61.9±7.6</td>
<td>0.085*</td>
</tr>
<tr>
<td>RRI，ms</td>
<td>779.1±141.2†</td>
<td>937.6±117.5†</td>
<td>0.000†‡</td>
</tr>
<tr>
<td>RRI-SD，ms</td>
<td>17.3±8.2†</td>
<td>24.4±8.3†</td>
<td>0.000†‡</td>
</tr>
<tr>
<td>RRI-CV，%</td>
<td>2.2±1.0†</td>
<td>2.6±0.9†</td>
<td>0.021†</td>
</tr>
<tr>
<td>RMSSD，ms</td>
<td>15.1±8.7†</td>
<td>19.2±9.5†</td>
<td>0.023†</td>
</tr>
<tr>
<td>BPsys，mmHg</td>
<td>143.3±27.4‡</td>
<td>132.2±26.8‡</td>
<td>0.048‡</td>
</tr>
<tr>
<td>Bpre，mmHg</td>
<td>78.9±18.3</td>
<td>72.6±10.7</td>
<td>0.079‡</td>
</tr>
<tr>
<td>呼吸频率，min^{−1}</td>
<td>17.0±3.5†</td>
<td>13.6±4.7†</td>
<td>0.000†‡</td>
</tr>
<tr>
<td>RRI-LF-功率，ms^{2}</td>
<td>182.2±211.8†</td>
<td>296.8±208.4†</td>
<td>0.000†‡</td>
</tr>
<tr>
<td>RRI-LFnu-功率，%</td>
<td>68.5±19.7‡</td>
<td>70.0±13.5‡</td>
<td>0.716‡</td>
</tr>
<tr>
<td>RRI-HF-功率，ms^{2}</td>
<td>69.2±61.5†</td>
<td>124.1±122.3†</td>
<td>0.005†‡</td>
</tr>
<tr>
<td>RRI-HFnu-功率，%</td>
<td>31.5±19.7‡</td>
<td>30.0±13.5‡</td>
<td>0.716‡</td>
</tr>
<tr>
<td>RRI 总功率，ms^{2}</td>
<td>251.2±232.7‡</td>
<td>424.0±277.8‡</td>
<td>0.001‡‡</td>
</tr>
<tr>
<td>RRI-LF/HF-ratios</td>
<td>5.0±6.5</td>
<td>3.5±3.3</td>
<td>0.909‡</td>
</tr>
<tr>
<td>BPsys-LF-功率，mmHg²</td>
<td>8.2±7.6</td>
<td>7.5±7.0</td>
<td>0.879‡</td>
</tr>
<tr>
<td>BPsys-HF-功率，mmHg²</td>
<td>3.0±6.1</td>
<td>1.6±1.9</td>
<td>0.463‡</td>
</tr>
<tr>
<td>BRS，ms-mmHg²</td>
<td>5.3±2.8‡</td>
<td>7.0±3.7‡</td>
<td>0.023‡‡</td>
</tr>
</tbody>
</table>

Hilz et al  High NIHSS Predicts Impaired CV Control

低频和高频波动的幅度是由 RRI (ms²/Hz) 和 BP(mm Hg²/Hz) 的功率谱密度曲线的整合决定的，并且被表述为 RRI(ms²) 和 BP(mm Hg²) 的低频和高频功率 [23,24]。

另外，我们计算 RRI-LF/HF 比率是交感神经活动的估计，并且，低频和高频功率的总和类似 RRI 振荡总功率，且是总体自我神经心脏调节的指标 [23,24]。我们正常化 RRI 低频和高频功率来降低个体间差异对 RRI-LF 及 RRI-HF 功率的总功率的影响 [26]。如下，RRI-LFnu=(RRI-LF/(RRI-LF+RRI-HF))×100%，RRI-HFnu=(RRI-HF/(RRI-LF+RRI-HF))×100% [23,24]。为确定 BRS，三角函数倒退光谱软件选择了有高度一致性 (>0.7) 的 BPsys 及 RRI 的 LF 和 HF 振荡配对 [27]。因为有着高度的一致性，压力感受器反射的敏感度可以看做是 Reader 及 BPsys 改变以及 BPsys 改变的增益值 [27]。

统计分析

对于数据分析，我们使用了商业适用统计程序 (SPSS 18.0, SPSS Inc.)。使用 Shapiro-Wilk 检验来检测数据是否呈正态分布。
The naming of the first occurrence of a stroke in June 2011.

The normal distribution of patients and controls used a t-test comparison. Non-normal data used the Mann-Whitney U test.

NIHSS and biological signals correlated with RRI and BRS.

We similarly used Spearman correlation to calculate the interval between stroke onset and NIHSS scores.

Results

In 50 stroke patients, NIHSS scores were between 1 and 21 (mean, 5; lower quartile, 3; upper quartile, 11). Table 1 described patient and control data.

In the group of patients, mean NIHSS scores were between 1 and 21 (mean, 5; lower quartile, 3; upper quartile, 11). Table 1 described patient and control data.

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讨论

与对照组相比,卒中患者有较高的血压、心率及呼吸频率,表明了增加的交感神经心血管调节[6,7,9,28-30]。然而,患者组较低的 RRI-LF 功率、较低的交感神经和副交感神经介导的 RRI-SDs、RRI-CVs 以及 RRI 总功率[23,24]表明自主神经心脏调节总的发生。患者组与对照组相比,有增高的血压、心率及呼吸频率。患者组与对照组有类似的 RRI-LF/HF 比率,表明卒中后交感神经-迷走神经平衡并没有很大的改变。尽管如此,在患者组,增高的 RRI-LF/HF 比率、高 NIHSS 评分以及较低的 RMSSD 及 RRI-HF 功率,证实了卒中后副交感神经调节失调,并且随着卒中中的严重性增加,交感神经调节失常占主要作用。


在我们的患者组中, NIHSS 评分与自主神经调节参数之间的关联 (见图),表明了在更严重的卒中患者中有更高的自主神经并发症风险。Tokgozoglu 等在 62 个卒中患者中观察到了突然死亡与副交感神经调节下降之间的一种联系,但是他们的交感神经功能增加[6]。7 个在院意外死亡的患者较其它的幸存患者有较高的 RRI-LF/HF 比率[6]。在 44 个卒中患者中, Orlandi 等发现 31 个有心律失常的患者中, RRI-LF/HF 比率增高[7]。

交感神经兴奋占主导地位,增加了卒中后快速性心律失常[10,12]、心肌梗死[10,12]、肌原纤维坏死、血管周围和间质纤维化以及心肌细胞空泡[10,32]的风险。它们额外的增加了二级脑损伤及水肿的风险。因为交感神经兴奋导致的高热炎性反应、高血糖、真性红细胞增多症及脑血管扩张,随后更进一步促进了心脑血管收缩[18,33,37,38]。因此,交感神经的输出增加危害卒中的预后[29]。

在我们的患者组中, 更严重的卒中患者逐渐下降的副交感神经兴奋, 增加了心血管及脑并发症的风险[34]。副交感神经的失调促进了恶性快速性心律失常[8,13,34,35]以及死亡率[16]。减少了动物卒中研究中的脑血管扩张,随后更进一步促进了脑血管收缩[37]及二级脑损伤[38]。

自主神经调节的总体失调,如高 NIHSS 评分的患者 RRI-SDs、RRI-总功率的下降,与逐渐增加的心脏并发症及突然死亡的风险相关[14,39]。
给主要的临床缺陷，而没有反应个体卒中患者（如失用症、神经认知缺损）的整体性[20,48]的不足。因此，卒中的严重性可以由相同的 NIHSS 评分但不同程度或不同部位的神经功能缺损而分类。相比之下，不同部分的中央自主神经调节网的参与很可能导致自主调节功能紊乱的不同以及反应自主调节失衡参数值的不同[49]。

然而，大部分自主调节参数值因年龄及性别的不同而有差异[50,51]，而 NIHSS 评分独立于患者的性别或年龄。除了 NIHSS 评分外，我们的患者年龄范围较广（48-84 岁），可能对自主调节参数的变异有影响。同样除了 NIHSS 评分外，类似性质的性别，25 个男性及 25 个女性卒中患者可能对自主调节参数的变异也有影响[50,51]。

自主调节参数的变异表明了对卒中患者进一步精确自主调节测试的必要性。然而，方法学上是不可行的。尽管对一个给定的 NIHSS 分数，自主神经调节参数变异范围较大，但是，自主调节参数与 NIHSS 评分之间的高度一致性仍然支持了这个结论。NIHSS 评分可以作为复杂的自主调节参数的替代方法。

总之，与先前研究一致[4-7,14,15,28]，我们的结果表明了对卒中患者进行自主神经功能监测的必要性，以进一步阻止因自主神经调节失败导致严重的并发症。

尽管如此，自主神经功能监测并不是广泛适用的。但是，NIHSS 评分是容易获得的。从我们患者的相关性来看，对于进展性的自主神经调节失败，NIHSS 评分可以作为一种替代方法。恶化的 NIHSS 评分需要更密切的关注心率、BP 以及这些值的差异。心率变异的下降以及血压变异的增加表明了增加的自主调节风险，并且预示着对心血管系统采取干预措施。

展望

在左半球或者右半球卒中后，有许多的研究报道了自主神经功能紊乱的不同[2,6,8,29,52]。尽管许多的研究发现，右半球卒中后，交感神经调节占主导地位[8,11,29,52,53]；但是，仍有报道称，在右半球卒中后，仅发现总的自主调节的下降或副交感输出下降[54]。然而，NIHSS 评分在左半球卒中的患者较右半球卒中的患者高[48,55,59]。

因此，我们假设 NIHSS 评分与自主神经功能参数可能是有半球优势的。自主神经功能调节的半球在左半球卒中患者较右半球卒中患者高。研究发现，右半球卒中后，交感神经调节占主导地位[8,11,29,52,53]；但是，仍有报道称，在右半球卒中后，仅发现总的自主调节的下降或副交感输出下降[54]。然而，NIHSS 评分在左半球卒中的患者较右半球卒中的患者高[48,55,59]。

因此，我们假设 NIHSS 评分与自主神经功能参数可能是有半球优势的。自主神经功能调节的半球优势[35]可能导致自主神经功能紊乱的差异，以及它们的联系对于 NIHSS 评分在右侧大脑中动脉或左侧大脑中动脉卒中患者的差异。我们的一项半球特异性的数据的初步分析显示，损伤半球与自主调节失衡的相互关系是错综复杂的。然而，它超出了此文章的范围并且讨论了半球特异性数据。我们将提供一份独立的详细的半球联系及差异的分析。

参考文献

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