Autonomic Shift and Increased Susceptibility to Infections After Acute Intracerebral Hemorrhage

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Background and Purpose—High infection rate after severe stroke may partly relate to brain-induced immunodepression syndrome. However, the underlying pathophysiology remains unclear. The aim of the current study was to investigate the role of autonomic shift in increased susceptibility to infection after acute intracerebral hemorrhage (ICH).

Methods—We retrospectively analyzed 62 selected patients with acute ICH from our prospective database. Autonomic shift was assessed using the cross-correlational baroreflex sensitivity (BRS). The occurrence and cause of in-hospital infections were assessed based on the clinical and laboratory courses. Demographic and clinical data including initial stroke severity, hemorrhage volume, intraventricular blood extension, history of aspiration, and invasive procedures such as mechanical ventilation, surgical hematoma evacuation, external ventricular drainage, central venous and urinary catheters, and nasogastric feeding were recorded and included in the analysis.

Results—We identified 36 (58%) patients with infection during the first 5 days of hospital stay. Patients with infections had significantly lower BRS, higher initial NIHSS scores, larger hemorrhages, and more frequently had intraventricular blood extension and underwent invasive procedures. In the multivariate regression model, decreased BRS (OR, 0.54; 95% CI, 0.32–0.91; P=0.02) and invasive procedures (OR, 2.32; 95% CI, 1.5–3.6; P<0.001) remained independent predictors for an infection after ICH.

Conclusions—Decreased BRS was independently associated with infections after ICH. Autonomic shift may play an important role in increased susceptibility to infections after acute brain injury including ICH. The possible therapeutic relevance of autonomic modulation warrants further studies. (Stroke. 2011;42:1218-1223.)

Key Words: autonomic □ baroreflex □ intracerebral hemorrhage □ infection □ stroke □ sympathetic

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cute stroke is associated with increased susceptibility to bacterial infection. Pulmonary and urinary infections are the most frequent medical complications after stroke and the leading cause of death, with prevalences of up to 33%. The pathophysiological mechanisms leading to high occurrence of infections after stroke are not fully understood. Poststroke pneumonia may result from aspiration caused by impaired consciousness or reduced bulbar reflexes with consecutive oropharyngeal dysphagia, as well as from invasive measures such as feeding tube placement or orotracheal intubation and mechanical ventilation. However, aspiration and specific neurological impairments alone do not completely explain the high incidence of poststroke infections. There is increasing evidence that brain–immune interactions become dysregulated after stroke, resulting in a stroke-related immunosuppression syndrome. Animal models of stroke and research in humans have well-documented stroke-induced immunodeficiency mediated via hypothalamic–pituitary axis and sympathetic nervous system activation. Catecholamine-mediated impairment of cellular immune responses include lymphopenia, decreased lymphocyte activation, shift from Th1 to Th2 cytokine predominance, or decreased HLA-DR expression on monocytes. Recently, suppressed neutrophil respiratory burst strongly correlated with catecholamine levels in subjects with hemorrhagic stroke. Accordingly, enhanced sympathetic activity with subsequent suppressed immune function has been associated with the occurrence of poststroke infections. Baroreflex sensitivity (BRS) is an established and reliable parameter to quantify the balance of autonomic nervous system noninvasively and has been clinically proven in numerous studies. Decreased BRS depicting sympathetic activation has been repeatedly found in acute ischemic and hemorrhagic stroke patients and is related to unfavorable outcome. Hence, we aimed to investigate if BRS measured on admission may predict the occurrence of in-hospital infections after acute hemorrhagic stroke.

Subjects and Methods

Population
From 2007 to 2010, 529 patients with acute intracerebral hemorrhage (ICH) admitted to our stroke unit or neurological intensive care unit (ICU) were screened for inclusion into an open prospective database.
This database prospectively collected consecutive patients with acute stroke meeting the criteria for nonbiased measurement of BRS as follows: at the time of the BRS measurement, all subjects had to be free of antihypertensive therapy or cardiovascular active treatment for at least 24 hours (except from urapidil). The type of previous antihypertensive therapy has been noted. Patients treated for acute hypertension on admission using bolus administration of parenteral urapidil, according to our local hospital protocol, were included and the use of urapidil was noted. The time delay between urapidil administration and BRS measurement had to be at least 1 hour. The urapidil use has not been defined as an exclusion criterion because it has been shown previously that it does not influence the baroreflex sensitivity when administered acutely.\textsuperscript{19,19}

Patients with a history of stroke, atrial fibrillation, myocardial infarction, diabetes mellitus, chronic renal failure, or other medical conditions known to affect autonomic functions are excluded from the BRS measurements, because these conditions may confound the results. For the purposes of the recent study, we retrospectively analyzed patients from the aforementioned database who fulfilled the following criteria: (1) acute ICH; (2) BRS measurement within the first 24 hours after onset of symptoms; and (3) no clinical or laboratory signs of infection on admission. At the time of the recent analysis, the database counted 67 patients with ICH. Two patients were excluded from the further analysis because of early mortality and 3 were excluded because of probable infection at admission (C-reactive protein [CRP] >50 mg/L). Thus, 62 patients entered the final analysis.

The diagnosis of ICH was confirmed by CT or MRI. The ICH volume was calculated from the first CT or MRI scan using the \( A \times B \times C \times 0.5 \) method, as described previously.\textsuperscript{19} For irregular shapes, the alternative formula \( A \times B \times C \times 0.33 \) was used.\textsuperscript{17,18} Additionally, the presence of intraventricular hemorrhage was recorded and scored using the LeRoux score. In this score, each ventricle is graded separately as: 1, trace of blood; 2, less than half the ventricle filled with blood; 3, more than half the ventricle filled with blood; and 4, ventricle filled with blood and expanded, resulting in maximum score of 16.\textsuperscript{19} At admission, patients were scored according to the NIHSS. History of hypertension and previous antihypertensive therapy was noted and included in the analysis. Demographic and basic clinical parameters were recorded.

Clinical Management

After BRS measurement at admission, uniform general management according to local guidelines was applied. This included close telemetric monitoring of blood pressure and treatment of hypertension using parenteral infusion of urapidil, clonidine, metoprolol, or diltiazem to achieve blood pressure values \(<160/90\) mm Hg. Orotracheal intubation and ventilatory support was initiated in patients with a Glasgow Coma Scale score \(<8\). In case of concomitant ventricular hemorrhage, placement of an external ventricular drain was performed. Hematoma evacuation was performed based on individual consensus between neurointensivist and neurosurgeon in patients with lobar superficial hematomas or in those deteriorating in the intensive care unit and at least 3 times per day on the stroke unit. Urine analysis and bacterial analysis of sputum was performed regularly twice per week, even if no clinical infection was suspected. In case of suspected clinical infection, chest radiographs, urine, blood, and sputum cultivations were performed. Antibiotic treatment was initiated if infection was clinically, radiologically, and laboratory confirmed and/or if fever \( >38.5^\circ C \), leukocytosis \( >12/\text{nL} \), and CRP \( >50\) mg/L were present in absence of a clear clinical focus.

Assessment of Infection

The charts and laboratory results have been reviewed up to 5 days (120 hours) after admission to identify infection. Recorded variables included presence of clinical signs of infections, CRP values on admission, leukocyte count and temperature on admission, the highest CRP value, leukocyte count and temperature within the first 5 days after admission, urine screening, chest radiographs, and antibiotic treatment. Based on the results, patients were classified into 4 groups as described previously.\textsuperscript{20} The first group included patients with pneumonia; diagnosis was based on clinical criteria including fever, purulent sputum, or respiratory deterioration and positive chest radiographs in combination with laboratory findings of leukocytosis and CRP \( >50\) mg/L.\textsuperscript{21,22} The second group comprised patients with urinary tract infections diagnosed based on elevated leukocyte count and positive nitrite in the urine screening in combination with leukocytosis and CRP \( >50\) mg/L. Because of high frequency of antibiotic treatment, we did not apply a positive urine culture as criterion.\textsuperscript{23} Patients who had empirical antibiotic treatment because of clinically suspected infection with elevated leukocyte count, CRP \( >50\) mg/L, and fever but without clearly identified focus during clinical follow-up were classified as being in the third group. The last group included patients without clinical and laboratory signs of infection during the first 5 days of hospital stay. Additionally, surgical evacuation of hematoma, external ventricular drain placement, the history of aspiration, ICU stay, mechanical ventilation, central venous and urinary catheters, nasogastric tube use, and antibiotic treatment in first 5 days of hospitalization were recorded. Because of the high colinearity between variables as ICU stay, mechanical ventilation, invasive catheters, and surgical treatment, we recomputed these variables for further analysis into an “invasiveness” score, giving 1 point for each procedure, including ICU stay, mechanical ventilation, central venous catheter, urinary catheter, nasogastric tube, external ventricular drain placement, and surgical removal of hematoma.

Assessment of Spontaneous BRS

Blood pressure for spontaneous BRS assessment was measured noninvasively using the Finometer device (FMS; Finapres Medical Systems BV). This device uses a volume clamp method to capture beat-to-beat (continuous) values of blood pressure and pulse rate in the finger artery. A cuff of appropriate size was attached to the middle finger of the nonhemiparetic hand of the patient in supine position and the hand was maintained at heart level. Using the Finometer device, continuous blood pressure and pulse rate for BRS assessment were recorded within 24 hours after stroke onset, usually on admission, for a period of 10 minutes. BRS was calculated using the sequential cross-correlation method.\textsuperscript{24} This method calculates the cross-correlation between a 10-second series of continuous systolic blood pressure and a 10-second series of interbeat intervals delayed by 0, 1, 2, 3, 4 and 5 seconds. The delay giving the highest correlation between the change in systolic blood pressure and the change in interbeat interval is selected if significant at a preset level \( P=0.01 \). Then, the regression slope is recorded as 1 BRS value. Subsequently, the process is repeated for series of systolic blood pressure and interbeat interval samples 1 second later. BRS gain values were expressed in ms/mm Hg.

Ethics

The local ethics committee approved the study. All patients or their next of kin gave written informed consent.

Statistics

Distribution of the data was visualized using histograms and tested using the 1-sample Kolmogorov–Smirnov test. For normally distributed data, the results are presented as mean, range, and SD; for non-normally distributed data, results are presented as median, range, and IQR. For comparison between the groups Fisher test, Mann–Whitney U test, or Student unpaired \( t \) test was used, as appropriate. Correlation analysis using Spearman or Pearson correlation coefficient was used to explore the univariate associations between the variables. Partial correlations and multivariate regressions were used to adjust for possible confounders. When significant in the univariate analysis, variables entered a stepwise logistic regression model to study the relationship between predictive variables and dependent variable as follows. A stepwise regression
Table 1. Demographic, Clinical, and Neuroradiological Characteristics of the ICH Population

<table>
<thead>
<tr>
<th>N</th>
<th>62</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (range; SD)</td>
<td>61.5 (17–86; 15.8)</td>
</tr>
<tr>
<td>Male</td>
<td>32 (51.6%)</td>
</tr>
</tbody>
</table>

**Etiology**
- Hypertensive: 36 (58.1%)
- Amyloid angiopathy: 8 (12.9%)
- Arteriovenous malformation: 8 (12.9%)
- Coagulopathy (including OAT): 5 (8%)
- Other defined: 1 (1.6%)
- Unknown: 4 (6.5%)

**NIHSS score at admission, median (range; IQR)**: 13.5 (1–34; 29)

**Hemorrhage volume (mL), median (range; IQR)**: 28.6 (0.3–234; 52.4)

**Localization**
- Lobar: 25 (40.3%)
- Deep: 34 (54.9%)
- Pons: 2 (3.2%)
- Cerebellar: 1 (1.6%)
- IVH extension: 31 (50%)
- LeRoux IVH score, mean (range; SD): 4.6 (0–16; 5.8)
- History of hypertension: 47 (75.8%)
- Previous antihypertensive therapy: 20 (32.2%)
- β-blockers: 9 (14.5%)
- Angiotensin-converting enzyme inhibitors/angiotensin-receptor antagonists: 20 (32.2%)
- Calcium channel antagonists: 8 (12.9%)
- Diuretics: 4 (6.4%)

ICH indicates intracerebral hemorrhage; IQR, interquartile range; IVH, intraventricular hemorrhage; NIHSS, National Institute of Health Stroke Scale; OAT, oral anticoagulant treatment.

Analysis was used to select which of the variables should be included in a regression model to predict the dependent variable. The procedure applied the variables 1 by 1 using a criterion such that the F statistic for the variable to be added must exceed the level of 0.05. After a variable was added to the model, the procedure analyzes all included variables and deletes any variable that fails to produce an F value <0.1. After necessary deletions are accomplished, a further variable can be added to the model. The procedure terminates when no variable outside the model exceeds the necessary threshold and every variable included is significant. Values of P<0.05 were considered statistically significant in all tests. All statistics were performed using statistical software SPSS 16.0 for Windows.

**Results**

Sixty-two patients with acute ICH met the inclusion criteria and entered the analysis. The demographic, clinical, and neuroradiological characteristics of the patient population are shown in Table 1. Median BRS at admission was 2.7 ms/mm Hg (range, 0.7–21.1; IQR, 3.2). Age, history of hypertension, and previous antihypertensive treatment including urapidil use on admission showed no influence on the measured BRS values. Thirty-three (53.2%) patients were treated in the ICU; of those, 31 (50%) required mechanical ventilation. All patients treated in the ICU received urinary catheters, central venous catheters, and nasogastric tubes. External ventricular drain placement was performed in 26 patients (42%) and hematoma was surgically removed in 16 (25.8%). Twenty-nine patients were treated in the stroke unit. Of those, 3 (10.3%) received central venous catheters, 14 (48.3%) received urinary catheters, and 4 (13.8%) received nasogastric tubes. Sixteen (26%) patients had a history suspect of aspiration. The median of the invasiveness score was 4 (range, 0–7; IQR, 5.25). Thirty-six (58%) patients had developed infection during the first 120 hours after admission. Thirty-one (50%) patients had pneumonia, 2 had urinary infections (3.2%), and 4 (6.4%) had clinical and laboratory signs of infection with no evident focus. There was no statistical difference in any of the clinical or neuroradiological variables between patients with pneumonia, urinary infection, or clinical laboratory signs of infection with no evident focus. However, this also may be attributable to the low frequencies in the infection subgroups other than pneumonia.

All 36 patients with infection received antibiotic treatment. Univariate analysis of variables associated with infection is shown in Table 2. We further performed a stepwise multivariate logistic regression model including the variables BRS, NIHSS score at admission, lesion volume, LeRoux intraventricular hemorrhage score, aspiration, and invasiveness score to predict infections. BRS (OR, 0.54; 95% CI, 0.32–0.91; P=0.02) and invasiveness score (OR, 2.32; 95% CI, 1.5–3.6; P<0.001) remained the only independent predictors for an early infection after ICH (Table 3). This model predicted 88.5% of all infections. Admission NIHSS score, hematoma volume, and intraventricular hemorrhage extension by LeRoux score correlated strongly with the invasiveness score (r=0.8 for NIHSS score at admission; r=0.7 for hematoma volume; r=0.7 for LeRoux intraventricular hemorrhage score; all P<0.001). Thus, removal of the invasiveness score from the model resulted in significance of the predictors BRS (OR, 0.64; 95% CI, 0.42–0.97; P=0.03), admission NIHSS score (OR, 1.1; 95% CI, 1.02–1.23; P=0.02), and LeRoux score (OR, 1.3; 95% CI, 1.01–1.6; P=0.04), with unchanged model fit predicting 88.5% of infections. Because of multicollinearity effects, aspiration did not remain an independent predictor of infection. Aspiration correlated with hemorrhage volume (r=0.26; P=0.04), with admission NIHSS score (r=0.34; P=0.005), with LeRoux intraventricular hemorrhage score (r=0.42; P=0.001), and with invasiveness score (r=0.42; P=0.001).

BRS correlated with intraventricular hemorrhage extension as quantified by LeRoux score (r=−0.38; P=0.003). BRS did not correlate with NIHSS score at admission or hemorrhage volume. Using a partial regression, we explored the relationship between BRS and intraventricular hemorrhage extension. LeRoux intraventricular hemorrhage score correlated with BRS independently of NIHSS score at admission and lesion volume (adjusted r=−0.38; P=0.003).

**Discussion**

Experimental and clinical evidence suggests that temporary immunodeficiency in acute stroke is mediated by enhanced sympathetic activation. Several studies found a strong association between high catecholamine levels and poststroke infections in patients with acute ischemic stroke.7–25 However, data for patients with ICH are missing. Most recently,
neutrophil respiratory burst has been found to be suppressed in patients with hemorrhagic stroke, correlating strongly with plasma noradrenalin concentration.5 In agreement with previous studies in ischemic stroke, we found decreased BRS mirroring autonomic shift toward sympathetic predominance to be independently linked to higher occurrence of infection after ICH. The relationship between autonomic shift and immunodepression seems plausible. The extensive sympathetic innervations of immune organs and the presence of adrenergic receptors on almost all types of leukocytes indicate that immune functions are strongly determined by the level of sympathetic activity.5 Experimental data show that prolonged exposure to catecholamines results in lymphocyte depletion, reduced NK-cell activity, decreased production of interferon-γ, IL-2 by Th1 helpers, and tumor necrosis factor-α, and IL-1β and IL-12 from monocytes.5,6 This phenomenon seems to be present through the whole spectrum of acute nervous system injuries, including ischemic stroke, traumatic brain injury, subarachnoid hemorrhage, or spinal cord injury.26

Interestingly, we found that autonomic shift is associated with higher frequency of infections independently of stroke severity or intracerebral blood volume. This finding is consistent with a previous study showing a relationship between catecholamines and poststroke infections that was independent of stroke severity.10 Interestingly, some small studies found a localization-dependent pattern in immune dysfunction after stroke.27,28 However, others did not confirm this finding.29 More importantly, previous studies investigated patients with ischemic stroke. In intracerebral hemorrhage, however, other factors such as intraventricular blood in the vicinity of autonomic and immunoregulatory centers (thalamus, hypothalamus, peri-aqueductal gray, formatio reticularis) may play a key role in sympathetic activation and, thus, in subsequent immunodepression. We found a strong relationship between intraventricular hemorrhage extension and sympathetic activation that was independent of hemorrhage volume and initial stroke severity.

Unlike in previous studies, there was no correlation between BRS and age or history of hypertension in our series.30,31 Thus, we assume that our cohort most likely was too small to show these effects, if present, presumably were overruled by the more profound baroreflex impairment related to stroke.14

Certain limitations of our study have to be acknowledged. First, it is the retrospective character of our study. The
retrospective identification and classification of infections have led to the fact that not all information required by standard scores, such as the Centers for Disease Control definitions of health care-associated infections, could be obtained.\textsuperscript{23} For example, the Centers for Disease Control criteria for urinary tract infection—dysuria, urgency, and frequency—cannot be assessed in sedated and ventilated patients or in patients with urinary catheters. Additionally, our protocol allowed classification of infections without microbiological confirmation. This may overestimate the occurrence of infections, because patients with probable or only possible infection according to current guidelines were included.\textsuperscript{21} However, it is a common difficulty in clinical studies that microbiological work-up frequently yields no specific result, possibly because of the early empirical antibiotic treatment for suspected infection, especially in ICU patients. Thus, it has been suggested previously that standard scores, such as the Centers for Disease Control criteria, may not be appropriate for ICU patients.\textsuperscript{21} Secondary, CRP elevation, leukocytosis, and fever may occur after stroke independently of infection, rendering a potential bias for accurate identification of infections. Therefore, we cannot completely exclude other mechanisms that may be responsible for the laboratory and clinical findings suggestive for an infection. This in particular holds true for the subgroup of patients without clearly identified infectious focus (group 3). However, 86.1% of the infected patients in our cohort had pneumonia, defined by a positive chest radiograph, and another 5.5% had positive urine findings. Third, because of the criteria for nonbiased BRS estimation, we excluded patients with previous stroke, myocardial infarction, atrial fibrillation, diabetes mellitus, or other conditions known to affect autonomic functions, as well as patients with actual antihypertensive treatment, thus producing a selection bias. This bias possibly limits the translation of our results into the general ICH population.

With accumulating evidence that sympathetic activation plays a central role in the immunodepression associated with central nervous system injury, the question of therapeutic targeting arises. Until now, studies investigating prophylactic antibiotic treatment after acute stroke rendered inconclusive results.\textsuperscript{5,24} Data on adrenergic blockade possibly ameliorating the consequences of sympathetic activation after stroke are scarce. In animals, the occurrence of bacterial infections after stroke can be prevented by administration of $\beta$-blockers.\textsuperscript{6} Interestingly, in a retrospective study, stroke patients with $\beta$-blocker treatment less often had pneumonia develop after stroke.\textsuperscript{34} Thus, hypothetically, the modulation of autonomic nervous system function, alone or in combination with prophylactic antibiotic treatment, may represent an attractive therapeutic option in preventing (not only) infective complications after stroke. Of clinical interest is that BRS may be used as a reliable marker for increased susceptibility to infections after acute stroke and may help to select patients suitable for intensive anti-infective prevention.

Conclusions

Decreased BRS was independently associated with infections after ICH. Autonomic shift may play an important role in increased susceptibility to infections after acute brain injury including ICH. The pathophysiology of ICH, however, may differ from ischemic stroke and other insults. In our study, autonomic shift in ICH was independently linked to intraventricular hemorrhage extension. The future therapeutic modulation of autonomic functions warrants further studies.

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Disclosures

None.

References


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