Systemic Inflammatory Response Depends on Initial Stroke Severity but Is Attenuated by Successful Thrombolysis

Heinrich J. Audebert, MD; Michaela M. Rott, MD; Thomas Eck, MD; Roman L. Haberl, MD

Background and Purpose—To determine whether body temperature, c-reactive protein (CRP), and white blood cell (WBC) count within the first days after stroke onset correlate with infarct size and stroke severity, and to examine whether successful thrombolysis reduces poststroke inflammation.

Methods—Out of 1500 consecutive acute ischemic stroke patients, 346 cases (43 patients with thrombolysis) were selected according to the following criteria: admission to hospital ≤24 hours after event, absence of prestroke and poststroke infectious disease, no intracerebral hemorrhage or brain stem stroke, and data availability. Body temperature, WBC within 3 days, and CRP within 5 days of event were determined daily. Lesion volume was measured by planimetry on computed tomography or MRI scans. Successful thrombolysis was defined as improvement on the National Institutes of Health Stroke Scale of ≥4 points within 24 hours.

Results—Increase of inflammatory parameters correlated significantly with lesion volume and stroke severity. This was shown for body temperature on days 2 and 3 (P<0.001), CRP on days 1 to 5 (P<0.05), and WBC on days 1 to 3 (P<0.01). Patients with successful thrombolysis had reduced body temperature on day 3, WBC on days 2 and 3, and CRP on days 3 to 5 (P<0.05).

Conclusions—Patients with a larger stroke volume and more severe stroke deficits have higher body temperature, CRP, and WBC count in the acute phase after stroke. Successful thrombolysis is related to a significantly attenuated inflammatory response. (Stroke. 2004;35:2128-2133.)

Key Words: c-reactive protein ■ cerebral infarction ■ inflammation ■ leukocytes ■ stroke, acute ■ temperature ■ thrombolysis

Stroke is known to produce an inflammatory response with an increase of white blood cell (WBC) count in peripheral blood1 as well as body core temperature2 and brain temperature.3 As a consequence of the association of increased body temperature and poor functional outcome, antibiotic treatment of infections and antipyretic treatment for elevated body temperature after stroke are recommended for the therapy of stroke patients in the acute phase.4,5

So far, little is known about the time course of most inflammatory parameters in the acute phase of ischemic stroke. This study was performed to assess the hypothesis that the systemic inflammatory response after stroke results from a response to the necrotic tissue itself but not from a cryptogenic infection. The correlation between lesion size and routinely available inflammatory parameters such as body temperature, c-reactive protein (CRP), and WBC was therefore analyzed. The inflammatory reaction seen in patients with initial ischemic deficit but reduced cerebral necrosis due to successful thrombolysis should be attenuated. Return of the acute phase parameters to normal ranges should occur earlier.

Methods

Patient Selection

Approximately 1500 consecutive stroke patients who were admitted to the Munich-Harlaching Hospital were screened in a retrospective analysis. Three hundred forty-six patients were selected according to the following criteria: admission ≤24 hours of event, accessibility of necessary clinical data, and computed tomography (CT) or MRI scans.

Exclusion criteria included intracerebral hemorrhage, including secondary hemorrhage on control CT/MRI (to avoid confounding effects of hematoma-induced inflammation); pre-existing and post-stroke infectious disease; brain stem stroke (because of difficult planimetry in CT scans and high risk of swallowing disorders); trauma and vascular events ≤4 weeks before stroke; vascular events <4 weeks before stroke; chronic inflammatory or malignant disease; and patients with antiinflammatory treatment (eg, corticoids, nonsteroidal antiinflammatory medication excluding aspirin).

Neuroradiological Data

CT scans were routinely done at hospital admission and repeated when symptom progression occurred or when no adequate lesion could be detected on the first scan. In patients with atypical findings, an MRI scan was performed. A neurologist and a radiologist who were blinded to the clinical course and the inflammatory parameters assessed stroke volume by CT planimetry using the formula de-
Exclusion of Prestroke and Poststroke Infections

All patients with anamnestic information about fever or any other inflammation ≤4 weeks before stroke were excluded. An analysis of the medical documentation was done to exclude poststroke infectious disease. According to the stroke unit protocol, a search for infectious diseases was started in patients presenting with clinically relevant symptoms or within laboratory parameters for suspicion of inflammation.

The measures consisted of a daily physical examination including chest auscultation. Chest radiography, urinalysis, and laboratory tests for systemic infection including complete blood count and CRP were performed routinely on admission. If patients showed clinical or laboratory signs of inflammation, such as fever, elevated WBC, CRP, purulent sputum, or clinical symptoms of urinary/pulmonary tract infections, the diagnostic procedures were repeated. In addition, urine or sputum cultures were performed depending on the clinical results. If fever exceeded ≥38.5°C, blood culture was taken to detect bacteraemia or systemic mycosis. The presence of urinary tract infection and appropriate clinical symptoms was defined as significant bacteriuria (≥10^5 cells/μL) or leukocyturia (≥20 cells per visual field). The diagnosis for pulmonary infection was established according to clinical and radiological findings (auscultation of rales, positive results of sputum culture, or radiological evidence of pulmonary infiltration).

Clinical Evaluation and Monitoring

The National Institutes of Stroke Scale (NIHSS) score was determined at hospital admission during the participation period in the German Stroke Databank. For correlation of stroke severity with inflammatory parameters, only patients without recombinant tissue plasminogen activator (rtPA) treatment were included.

In all patients who received systemic rtPA, NIHSS score was assessed on admission and 24 hours after thrombolysis. Systemic thrombolysis was performed according to the National Institute of Neurological Disorders and Stroke (NINDS) protocol. Successful thrombolysis was defined as an NIHSS-improvement of ≥4 points within 24 hours.

According to the stroke unit protocol, body temperature was measured on admission and during the subsequent 3 days with intervals between 2 and 12 hours, depending on temperature elevation. Measuring temperature was performed orally or rectally. If patients could not cooperate sufficiently (eg, complete occlusion of the mouth), only rectal measurements were recorded. Patients with a temperature of ≥37.5°C were treated with paracetamol or metamizol (oral, rectal, or IV administration) according to the stroke unit protocol. For statistical analysis, the earliest body temperature recorded on day of admission and the highest temperature on days 2 and 3 were determined.

Laboratory Analysis

WBC (normal range, 4.0 to 10.0/μL) and CRP (normal range, <0.5 to 0.8 mg/dL) were determined using routine laboratory methods. For statistical analysis, WBC and body temperature on hospital admission and on days 2 and 3 were determined. CRP was measured on admission and on days 2 to 5. For all CRP values <0.5 mg/dL, a value of 0.4 mg/dL was used for statistical tests.

Statistical Analysis

Statistical analysis was performed using Microsoft Excel and SPSS software. Spearman correlation coefficient and the Mann–Whitney U test were used to determine the correlation between stroke volume and inflammatory parameters. Differences between NIHSS scores were assessed applying Fisher exact test. The findings were considered statistically significant when the probability value was <0.05.

Results

Epidemiological and clinical data are shown in Table 1.

Correlation of Inflammatory Parameters and Stroke Volume

Temperature, Antipyretic Treatment, and Stroke Volume

Spearman correlation coefficient yielded significant values (P<0.001) for body temperature on days 2 and 3 and the number of antipyretics administered within the first 48 hours (Table 2).

CRP, WBC, and Stroke Volume

CRP and stroke volume showed a significant correlation using Spearman correlation coefficient for all 5 days (day 1, P<0.05; days 2 to 5, P<0.001). The results for the correlation between WBC and stroke volume were significant for the 3 assessed days (day 1, P<0.01; days 2 and 3, P<0.001).

Correlation Between Initial Stroke Severity and Inflammatory Parameters

Spearman correlation coefficient indicated that more severe strokes were associated with a higher leukocyte count from the first day forward (day 1, P<0.01; day 2, P<0.001; day 3, P<0.05). NIHSS score on admission was significantly correlated with body temperature on days 2 and 3 (P<0.001) and N° of administered antipyretic drugs within 48 hours (P<0.01) (Figure 1). Similar results were found for the increase of CRP on day 2 (P<0.01), day 4 (P<0.05), and day 5 (P<0.01).

Patients With and Without Successful Thrombolysis

Sixty-five patients received systemic rtPA treatment. Forty-three patients were selected in the analysis according to the inclusion criteria. Twenty-three patients (group A) were treated successfully with a median NIHSS score at admission of 10.0±3.4 and median NIHSS score 24 hours later of

<table>
<thead>
<tr>
<th>TABLE 1. Epidemiological and Clinical Data</th>
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<tbody>
<tr>
<td>Total N=346</td>
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<tr>
<td>Age</td>
</tr>
<tr>
<td>Infarct volume, mL</td>
</tr>
<tr>
<td>Delay between onset and admission, h</td>
</tr>
<tr>
<td>Antipyretic treatment ≤48 h, in 138 patients</td>
</tr>
</tbody>
</table>

scribed by Kothari et al: Vol (ml)=[A(mm)×B(mm)×C(mm)]/2. A is the greatest diameter by CT, B is the diameter 90° to A, and C is the approximate number of CT slices with lesion multiplied by the slice distance. To assure the comparability of the assessment, the CT scans of 23 patients were measured by both the neurologist and the radiologist. There was a high level of agreement between both investigators with an intraclass correlation coefficient of 0.9504 (98% CI). CTs used for planimetry (N=281) were performed 1 to 5 days after stroke onset. Infarct volume on MRI scans (N=65) was measured in T2 and fluid-attenuated inversion recovery images. Residual lesions of former cerebral infarcts were not included.
2.0±2.7. Twenty patients (group B) did not have a significant improvement (median NIHSS score of 15.0±4.6 at admission and 16.5±9.3 24 hours after thrombolysis). The differences between the NIHSS scores at admission ($P<0.05$) and 24 hours after thrombolysis ($P<0.001$) were statistically significant. Lesion volumes in control CT/MRI (days 2 to 5) were larger in group B (mean value 140.8±137 mL versus 36.2±46 mL).

Baseline parameters of temperature, WBC, and CRP were similar in groups A and B. Differences between groups A and B are listed in Table 3. The correlation between inflammatory parameters and time course after stroke are shown in Figure 2.

### Discussion

Elevation of inflammatory parameters in the acute phase of ischemic stroke is a well-known phenomenon and may result from infectious complications or from the inflammatory reaction of the damaged brain tissue. Necrotic tissue is eliminated by cellular, humoral, and metabolic mechanisms, which are all part of the inflammatory reaction.7 Previous studies have already shown that high systemic inflammatory parameters, especially high body temperature, are associated with the clinical severity and outcome of stroke. This increase in body temperature starts within 24 hours of the event, whereas fever due to infections seems to have a later onset.2,8–10

This is a retrospective analysis that contains some limitations. Concomitant infections cannot be excluded totally, despite the standardized protocol. Accuracy of overall temperature measurement depends on correctness of the assessments. Oral and rectal measures are widely comparable if conducted properly.

In our sample of ischemic stroke patients without evidence of infection, the elevation of body temperature and WBC (within the first 3 days) as well as CRP (within the first 5 days) were significantly correlated with initial stroke severity and the resulting stroke volume. The number of antipyretic drugs administered within the first 48 hours was also increased in patients with larger lesion size. Correlation with infarct volume was highly significant for body temperature on days 2 and 3 as well as for the number of antipyretic drugs ($P<0.001$) and for WBC for all assessed days. CRP and stroke volume revealed a significant correlation using Spearman correlation coefficient for all 5 days.

### Table 2. Results of Correlations

<table>
<thead>
<tr>
<th></th>
<th>Infarct Volume</th>
<th>NIHSS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Spearman-Rho</td>
</tr>
<tr>
<td>Temperature</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>290</td>
<td>0.077</td>
</tr>
<tr>
<td>Day 2</td>
<td>292</td>
<td>0.421</td>
</tr>
<tr>
<td>Day 3</td>
<td>264</td>
<td>0.472</td>
</tr>
<tr>
<td>$\Sigma$ Antipyretics</td>
<td>301</td>
<td>0.444</td>
</tr>
<tr>
<td>WBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>318</td>
<td>0.154</td>
</tr>
<tr>
<td>Day 2</td>
<td>264</td>
<td>0.396</td>
</tr>
<tr>
<td>Day 3</td>
<td>184</td>
<td>0.371</td>
</tr>
<tr>
<td>CRP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>308</td>
<td>0.122</td>
</tr>
<tr>
<td>Day 2</td>
<td>253</td>
<td>0.334</td>
</tr>
<tr>
<td>Day 3</td>
<td>176</td>
<td>0.417</td>
</tr>
<tr>
<td>Day 4</td>
<td>146</td>
<td>0.366</td>
</tr>
<tr>
<td>Day 5</td>
<td>127</td>
<td>0.390</td>
</tr>
</tbody>
</table>

**Figure 1.** Correlation between NIHSS score and temperature or WBC on day 2.
CRP and WBC seem to be very early indicators for lesion size, especially because the value assessed for day 1 was the first measured after hospital admission.

Elevated Body Temperature and Lesion Size

Other authors have already demonstrated that high body temperature in the acute phase of ischemic stroke is associated with neurological deficit, clinical progression, bad outcome, and increased lesion size.\textsuperscript{2,8–18} The crucial point for prognostic relevance is the early increase in body temperature. It is also known that in acute stroke intracerebral temperature is usually higher than body core temperature.\textsuperscript{3} Moderate hypothermia as a therapeutic option is associated with a higher rate of infectious complications.\textsuperscript{3,19}

Our results yield an association between lesion size and body temperature on the second and third days, which is confirmed by the association between lesion size and number of antipyretic drugs administered within the first 48 hours. In our cohort there was no significant correlation between lesion size and first measurement of body temperature after hospital admission (mean 6.7 hours after stroke onset). Boysen and Christensen demonstrated that body temperature starts to rise within 4 to 6 hours after onset. A significant correlation with a bad outcome was found for body temperature after 10 to 12 hours,\textsuperscript{2} several hours later than the average in our analysis.

Elevated CRP and Lesion Size

There are no reports so far on the association between lesion size and elevated CRP in the acute phase of ischemic stroke. We found a significant correlation between lesion size and CRP in the first 5 days after onset. Clinical stroke severity was correlated with increased CRP levels on days 2, 4, and 5. The studies conducted so far analyzed the prognostic value of CRP for progression and outcome.\textsuperscript{20–22} Whereas Canova et al\textsuperscript{23} came to the conclusion that CRP at hospital admission was not suitable for predicting outcome, Napoli et al\textsuperscript{22,24} found an association between elevated CRP within the first 48 hours and bad outcome.

Elevated White Blood Cell Count and Lesion Size

Several studies have already been conducted concerning the association between WBC count and lesion size. In some of them, leukocyte migration and accumulation was measured using leukocytes labeled with radioactive markers and \( \gamma \) scintigraphy or single-photon emission computed tomography. In animal models as well as in humans these leukocytes migrate and accumulate in the damaged tissue after ischemic stroke. Accumulation progressively increases during the first 6 to 24 hours after onset, remains at a high level for 6 to 9 days, and then decreases but stays measurable for up to 5 weeks.\textsuperscript{25–27} The activation of leukocytes is accompanied by an increase of WBC in the peripheral blood.\textsuperscript{1,20,25,26,28,29} The prognostic value of this leukocytosis for outcome and its association with clinical extent (but not with infarct size) has already been investigated.\textsuperscript{1,25,30–32} The analysis of single-photon emission computed tomography imaging and WBC also indicates that there may be an association between leukocyte activation in the brain and the resulting stroke volume.\textsuperscript{25} Silvestrini et al\textsuperscript{32} reported that WBC and leukocyte aggregation in the peripheral blood of stroke patients were significantly higher than in the control group, and that leukocyte aggregation (but not leukocyte count!) was significantly higher on days 2 and 4 for patients with large infarctions than for patients with small lesions. Emsley et al\textsuperscript{33} investigated the time course of peripheral inflammatory parameters such as CRP and WBC in a small sample of acute stroke patients and reported elevated levels until 3 months after stroke.
In our analysis, we found a significant correlation between stroke volume or stroke severity and the increase of WBC in the peripheral blood for the first 3 days. This result is consistent with the temporal profile of leukocyte accumulation in the damaged brain tissue as demonstrated by Akopov et al. In the subgroup of patients treated with systemic thrombolysis, patients with a clinically significant improvement of neurological functions developed a significantly attenuated inflammatory reaction. The induced salvage of brain tissue can be interpreted as a model of reduced systemic inflammation by avoiding cerebral necrosis.

Conclusions
Necrosis in the brain produces a strong inflammatory reaction. Therefore, the association between lesion size and elevated inflammatory parameters is a sufficient explanation of previous observations that elevated inflammatory parameters in acute stroke patients are predictive for the functional outcome.

Tissue necrosis in the brain initiates fever, CRP elevation, and WBC elevation, which can be measured as a systemic inflammatory response. The activation of cellular, humoral, and metabolic mechanisms in the brain results in an inflammatory reaction, which may lead to an increase of necrotic tissue in the tissue at risk (ischemic penumbra). Apart from these deleterious effects, neuroprotective mechanisms of inflammation are being discussed.

Possible Implications for Clinical Decision Making
Considering that inflammatory parameters correlate with lesion size, diagnosis and therapy of suspected infectious complications in stroke patients can be interpreted in a differentiated way. In patients with small lesions, a marked increase of body temperature, CRP, or WBC should be taken as an indicator for infection. On the other hand, patients with large lesions often show a moderate increase of inflammatory parameters but a search of possible infections does not yield positive results. In these cases, antibiotic treatment should be considered very carefully, taking into account possible side effects and costs of treatment. Moreover, patients with larger lesions may show a slower decrease of inflammatory parameters because of the cerebral necrosis rather than because of insufficient antibiotic treatment.

The postulated negative effects of the inflammatory reaction on the penumbra could possibly be prevented by an antiinflammatory treatment in the acute phase of stroke. Such a treatment in the very early, ideally in the preclinical, phase might help prevent this secondary cell damage. Drugs with an antipyretic as well as antiphlogistic effect would be suitable.

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