Extracorporeal Rheopheresis in the Treatment of Acute Ischemic Stroke
A Randomized Pilot Study

Jörg Berrouschot, MD; Henryk Barthel, MD; Johannes Köster, MD; Swen Hesse, MD; Annegret Rössler, MD; Wolfram H. Knapp, MD; Dietmar Schneider, MD

Background and Purpose—Extracorporeal rheopheresis is a safe method to optimize hemorheology. Our aim was to determine whether treatment with extracorporeal rheopheresis in patients with acute ischemic hemispheric stroke improves cerebral perfusion as assessed with serial ⁹⁹ᵐTc–ethyl-cysteinate-dimer single-photon emission CT (⁹⁹ᵐTc-ECD SPECT). We also investigated how clinical outcome is associated with treatment and imaging results.

Methods—Thirty-three patients (mean age, 64±10 years) with acute ischemic hemispheric stroke were included in a prospective, randomized, parallel group pilot study. First treatment with or without extracorporeal rheopheresis took place within 12 hours after the onset of symptoms and was repeated 3 times at intervals of 24 hours. Hemorheological parameters were measured before and after each session. Each patient underwent ⁹⁹ᵐTc-ECD SPECT immediately before treatment, 6 to 8 hours after treatment, and after 5 days. A semiquantitative SPECT graded scale was used to measure depth and extent of activity deficits and thus to quantify the perfusion deficit.

Results—Seventeen patients were actively treated with extracorporeal rheopheresis, and 16 patients did not receive extracorporeal rheopheresis. After 3 months, no differences were found in the functional or neurological outcome. Despite a rapid, sustained decrease of plasma viscosity and erythrocyte aggregation in the rheopheresis group, there was no significant difference in the SPECT graded scale after therapy between the 2 groups. Patients with early reperfusion (decrease in the SPECT graded scale >25% 6 to 8 hours after therapy compared with the baseline examination) experienced a better functional outcome (Modified Rankin Scale) after 3 months compared with patients without reperfusion (P=0.04).

Conclusions—Since quantitative flow mapping and clinical follow-up did not reveal any differences between patients who were treated with extracorporeal rheopheresis and controls, it appears very unlikely that extracorporeal rheopheresis enhances reperfusion after acute cerebral ischemia. (Stroke. 1999;30:787-792.)

Key Words: rheology ■ stroke, ischemic ■ tomography, emission computed ■ viscosity

In a previous study we showed that extracorporeal membrane differential filtration (rheopheresis) is a safe method to optimize hemorheology in patients with acute ischemic stroke.¹ Extracorporeal rheopheresis quickly and effectively lowers plasma viscosity and erythrocyte aggregation without affecting the hematocrit, so that the oxygen transport capacity for the ischemic brain remains constant, in contrast to widespread hemodilution.

Single-photon emission CT (SPECT) can be used to assess impaired perfusion in the acute stage of ischemia and during follow-up. The retention of tracer ⁹⁹ᵐTc–ethyl-cysteinate-dimer (⁹⁹ᵐTc-ECD), however, not only reflects cerebral perfusion but also intact cerebral metabolism.²,³ The aim of this study was to investigate whether treatment with extracorporeal rheopheresis in patients with acute ischemic hemispheric stroke improves cerebral perfusion as assessed with serial ⁹⁹ᵐTc-ECD SPECT, and how clinical outcome is associated with treatment and imaging results.

Subjects and Methods
From March 1996 to December 1997, 33 patients (mean age, 64±10 years) at our Neurological Critical Care Unit were included in this prospective, randomized, parallel group pilot study. Inclusion criteria were as follows: age 18 to 80 years, sudden onset of a focal neurological deficit in the territory of the middle cerebral artery (MCA), Scandinavian Stroke Scale score (46 points maximum, without “gait”), 40 points, normal CT or slight hypodensity of <33% of the MCA territory, and an activity deficit in the territory of the MCA on the baseline ⁹⁹ᵐTc-ECD SPECT to rule out transient ischemia or minor stroke.² Treatment with or without extracorporeal rheopheresis had begun within 12 hours after the onset of symptoms. Exclusion criteria were as follows: coma, previous stroke, severe

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TABLE 1. Demographic and Clinical Findings of Active Treatment and Control Groups

<table>
<thead>
<tr>
<th></th>
<th>Extracorporeal Rheopheresis (n=17)</th>
<th>Controls (n=16)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63±9</td>
<td>65±12</td>
<td>0.5</td>
</tr>
<tr>
<td>Male</td>
<td>12 (71%)</td>
<td>10 (63%)</td>
<td>0.5</td>
</tr>
<tr>
<td>On admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>159±20</td>
<td>167±15</td>
<td>0.2</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>7.8±2.9</td>
<td>8.0±2.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Time from onset of symptoms to start of therapy, min</td>
<td>390±60</td>
<td>400±60</td>
<td>0.9</td>
</tr>
<tr>
<td>SSS on randomization, points</td>
<td>29±7</td>
<td>28±7</td>
<td>0.9</td>
</tr>
<tr>
<td>SSS day 5, points</td>
<td>30±13</td>
<td>29±13</td>
<td>0.8</td>
</tr>
<tr>
<td>Outcome day 90±14</td>
<td>Modified Rankin Scale</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Modified Rankin Scale 0–1</td>
<td>4 (24%)</td>
<td>4 (25%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Barthel Index</td>
<td>59±40</td>
<td>58±36</td>
<td>0.9</td>
</tr>
<tr>
<td>Mortality</td>
<td>3 (18%)</td>
<td>3 (19%)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

SSS indicates Scandinavian Stroke Scale.

cardiac insufficiency (New York Heart Association class III or IV), acute infection, and contraindications against therapeutic heparinization.

The patients underwent first extracorporeal rheopheresis within 12 hours after the onset of symptoms, second treatment 12 to 24 hours after first treatment, and third and fourth treatments 24±3 hours after previous treatment. No thrombolytic or neuroprotective drugs, drugs affecting hemorheology, platelet aggregation inhibitors, or anti-thrombotic drugs (with the exception of heparin) were permitted.

Computed CT

Baseline CT was performed before the start of treatment, with follow-up CTs after the first treatment session and on day 5. For detection of early infarction signs (parenchymal hypodensity or focal swelling), the baseline CT was used. The size of infarction and hemorheologic transformation (according to the European Cooperative Acute Stroke Study I [ECASS-I] classification: hemorheic infarction HI 1 or HI 2 and parenchymal hemorrhage PH 1 or PH 2<sup>±6</sup>) were determined on the follow-up CT.

99mTc-ECD SPECT

The 99mTc-ECD studies were performed with the use of a brain-dedicated SPECT camera (Ceraspect, DSI) with 3 rotating parallel hole collimators. 99mTc-ECD (400 MBq) was used for the first SPECT examination before therapy started. Six to 8 hours after the first extracorporeal rheopheresis, a first SPECT control was performed with 600 MBq 99mTc-ECD, with a second one (600 MBq 99mTc-ECD) after the end of treatment on day 5. The SPECT examinations for the control group were performed at the same time as those for the active treatment group. The method and evaluation technique used have been described in detail in a previous report.4

For semiquantitative region of interest (ROIs) analysis of all 3 SPECT studies, 5 transverse and 3 coronal slices were selected in each patient at predefined distances from the commissura anterior–commissura posterior line (transverse slices: Talairach coordinates = –20 mm, +1 mm, +8 mm, +21 mm, +34 mm) and from the line perpendicular to the commissura anterior–commissura posterior line cutting the commissura anterior (coronal slices: Talairach coordinates5 mm, –16 mm, –37 mm), respectively. In these 8 slices, 88 ROIs were generated with the use of a commercial program (Ceraspect, DSI) and were assigned to anatomic structures according to the stereotaxic atlas of Talairach and Tournoux.2 Count densities of ROIs of the symptomatic hemisphere were related to those of the corresponding contralateral regions and classified as abnormal if a deficit was >10% (ratio ≥0.90), in agreement with widely accepted standards.8 In accordance with Hanson et al,9 we used the SPECT graded scale, a measure of the intensity and spatial extent of activity deficits (respective ischemia). Each ROI was given a score of 0 to 9, where 0 indicated a ratio ≥0.91, 1 a ratio of 0.81 to 0.90 (corresponding to 81% to 90% activity compared with the contralateral side), 2 a ratio of 0.71 to 0.80, etc. The scores for all the individual ROIs were added to produce the SPECT graded scale. Early and late reperturbation were defined as a decrease in the SPECT graded scale >25% between baseline and the first or second control.10,11 SPECT analysis was performed by blinded observers with respect to the type of therapy and the clinical outcome.

TABLE 2. Hemorheological Findings of the Active Treatment Group and the Control Group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>First Treatment &lt;12 h After Onset of Symptoms</th>
<th>Second Treatment 12–24 h After 1st Treatment</th>
<th>Third Treatment 24±3 h After 2nd Treatment</th>
<th>Fourth Treatment 24±3 h After 3rd Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Extracorporeal rheopheresis (n=17)</td>
<td>Plasma viscosity, mPa · s</td>
<td>1.31±0.09</td>
<td>1.14±0.05</td>
<td>1.16±0.06</td>
</tr>
<tr>
<td></td>
<td>RBC aggregation, 3/s</td>
<td>27±11</td>
<td>16±6</td>
<td>20±7</td>
</tr>
<tr>
<td></td>
<td>RBC count, 10&lt;sup&gt;12&lt;/sup&gt;/L</td>
<td>4.5±0.4</td>
<td>4.7±0.4</td>
<td>4.4±0.4</td>
</tr>
<tr>
<td></td>
<td>Hematocrit</td>
<td>0.42±0.03</td>
<td>0.44±0.03</td>
<td>0.41±0.03</td>
</tr>
<tr>
<td></td>
<td>Fibrinogen, g/L</td>
<td>3.1±0.7</td>
<td>1.8±0.4</td>
<td>2.2±0.6</td>
</tr>
<tr>
<td>Controls (n=16)</td>
<td>Plasma viscosity, mPa · s</td>
<td>1.35±0.09</td>
<td>1.36±0.13</td>
<td>1.33±0.08</td>
</tr>
<tr>
<td></td>
<td>RBC aggregation, 3/s</td>
<td>29±9</td>
<td>35±6</td>
<td>31±10</td>
</tr>
<tr>
<td></td>
<td>RBC count, 10&lt;sup&gt;12&lt;/sup&gt;/L</td>
<td>4.5±0.6</td>
<td>4.4±0.9</td>
<td>4.4±0.7</td>
</tr>
<tr>
<td></td>
<td>Hematocrit</td>
<td>0.42±0.05</td>
<td>0.41±0.08</td>
<td>0.4±0.06</td>
</tr>
<tr>
<td></td>
<td>Fibrinogen, g/L</td>
<td>3.3±0.8</td>
<td>3.4±0.9</td>
<td>3.3±1.0</td>
</tr>
</tbody>
</table>

RBC indicates red blood cell.
and a rheofilter (Cascadeflo AC-1760, Asahi Medical Co). After separation of the plasma, it was pumped through the rheofilter; molecules <900 000 Da were returned to the patient, whereas the high-molecular-weight components of the plasma were retained in the hollow fibers of the rheofilter. The exact procedure is described elsewhere.1

During the entire treatment period, intravenous anticoagulation with heparin (doubling of the partial thromboplastin time) was performed for both patients with extracorporeal rheapheresis and patients of the control group.

The following laboratory parameters were measured before and after each extracorporeal rheapheresis and at parallel times for the patients of the control group: plasma viscosity (capillary tube plasmaviscosimeter, Fresenius; normal range, 1.17 to 1.31 mPa·s), erythrocyte aggregation (Mini-Aggregometer, Myrenne; normal range at 3/s, 16 to 37), hematocrit (Coulter STKS, Coulter; normal range, 0.37 to 0.52), red blood cell count (Coulter STKS, Coulter; normal range, 4.2 to 6.0 10¹²/L), and fibrinogen (CA 5000, DADE; normal range, 1.5 to 4.5 g/L).

Clinical Investigations and Follow-Up

Scores on the Scandinavian Stroke Scale were determined before the start of therapy, on day 5, and after 90±14 days. Patients who died received 0 points. On day 90±14, scores on the Barthel Index and the Modified Rankin Scale were determined by one of the examiners (A.R.), who was not aware of the kind of treatment the patients received.

Statistical Analysis

Clinical data, SPECT, and CT findings between the 2 groups were compared with the Mann-Whitney U test, the Student’s t test for unpaired data, and the χ² test. For paired samples the Wilcoxon test was used. For laboratory values a level of significance of 0.01 was selected; a level of 0.05 was selected for all other values.

Results

Demographic and Clinical Findings

Seventeen of 33 patients were treated with and 16 without rheapheresis. The 2 groups did not differ in terms of demographic findings, vital parameters, or the severity of neurological deficit on admission (Table 1). Therapy was commenced on average 6.5 hours after the onset of symptoms (range, 4 to 9 hours).

<table>
<thead>
<tr>
<th>TABLE 2. Continued</th>
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<tr>
<td>Reduction, %</td>
</tr>
<tr>
<td>18</td>
</tr>
<tr>
<td>55</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>55</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>+12</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
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<tr>
<td>+15</td>
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</table>

There were no statistical differences in neurological or functional outcome between the 2 groups after 5 days or after 3 months (Table 1). Three patients in each group died. Four patients (2 in each group) died of space-occupying brain edema caused by the ischemic infarction between day 5 and 10. The other 2 patients died of pneumonia after 46 and 74 days.

Hemorheological Findings

Treatment with extracorporeal rheapheresis produced an immediate reduction of plasma viscosity (18% reduction), red blood cell aggregation (55% reduction), and fibrinogen (58% reduction) sustained throughout the entire period of treatment. Red blood cell counts and hematocrit did not change. In the control group, the rheological parameters remained constant throughout the entire treatment period (Table 2).

CT Findings

Twenty patients (61%) (12 rheapheresis, 8 controls) had early infarct signs in the baseline CT. In the follow-up CT after 5 days, no infarct signs were found in 3 patients, 11 patients had infarcts <33% of the MCA territory, 8 patients had infarcts 33% to 66% of the MCA territory, and 11 patients had infarcts >66% of the MCA territory. There was no statistical difference between actively treated patients and controls with respect to infarct size (Table 3).

Twelve patients (36%), 6 in each group, had a hemorrhagic transformation, including 1 patient in the control group with PH 2 and clinical deterioration.

Semiquantitative ⁹⁹ᵐTc-ECD SPECT Findings

There was no difference in the SPECT graded scale changes between patients treated with extracorporeal rheapheresis and...
patients of the control group. Although patients in the control group experienced on average a greater improvement of the SPECT graded scale, the difference was not statistically significant (Table 3).

Patients with early reperfusion (6 to 8 hours after therapy) had a better functional outcome after 3 months than patients without (Table 4). Of the 6 patients with early reperfusion who had a good functional outcome (Modified Rankin Scale 0 to 1), 3 patients were actively treated and 3 were controls.

**Discussion**

The results of this study do not lend support to the hypothesis that optimization of hemorheology (namely of plasma viscosity and red blood cell aggregation) leads to an improvement of cerebral blood flow and cerebral metabolism in patients with hemispheric ischemic stroke. To date, a large number of studies on the effectiveness of hemodilution in acute ischemic stroke have been performed. None of these studies has demonstrated the efficacy of this therapy principle. One possible reason is the time window, which may still be too large. Indeed, in a study based on animal experiments in which hemodilution was started within 3 hours after the onset of symptoms, the size of the infarct was shown to have been reduced and the neurological outcome improved. Another possible reason is that pure rehydration alone in the placebo group obviously had a beneficial effect, and, particularly in patients with hematocrit ≥45%, seems to have a better effect than hemodilution. Furthermore, blame has been placed on the limited reduction of hematocrit, although the optimum hematocrit (ie, that which facilitates the best possible flow properties of the blood and sufficient oxygen transport capacity) for humans with ischemic stroke is not known. An increase in cerebral blood flow is not a result of the improved rheological properties of blood but rather vasodilatation owing to the lower oxygen supply and the shift of the oxygen dissociation curve. In the ischemic tissue, where the vessels undergo maximum dilatation as a result of acidois, an additional increase in blood flow is not possible, and the reduction of oxygen transport capacity tends to lead to a further drop in oxygen tension in the cerebral tissue.

The main target of a rheological therapy approach should therefore not be the hematocrit (whole blood viscosity, more influence on macrocirculation) but rather plasma viscosity and erythrocyte aggregation (more influence on microcirculation). Reduced plasma viscosity lowers vessel resistance (Hagen-Poiseuille’s law) and thus raises cerebral blood flow (Ohm’s law). Using extracorporeal rheopheresis, we were able to quickly and lasting reduce plasma viscosity and erythrocyte aggregation by the selective elimination of high-molecular-weight proteins (fibrinogen, \( \alpha_2 \)-macroglobulin), lipoproteins, and cholesterol. This approach is designed to improve not only the flow characteristics in microcirculation but also the disrupted erythrocyte-endothelium interaction. There are currently no comparable studies in the literature. Rubba et al demonstrated an increase in blood flow velocities in transcranial Doppler after LDL apheresis in patients with familial hypercholesterolemia that they attributed to the restoration of endothelium-mediated vasodilation, which is inhibited by a high concentration of LDLs.

To examine the effect of the hemorheological treatment approach on cerebral blood flow and ultimately on cerebral metabolism, we chose \( ^{99m} \text{Tc-ECD} \) SPECT examinations. SPECT can be performed easily and in a well-reproducible manner in the acute setting of ischemic stroke patients. In a number of studies, semiquantitative SPECT analyses were used for interindividual and intraindividual follow-up studies in ischemic stroke patients. In contrast to \( ^{99m} \text{Tc-hexamethy]propyleneamine oxime,} \( ^{99m} \text{Tc-ECD} \) is not purely a perfusion marker but also seems to depend on the intact cerebral metabolism. Consequently, use of the term “reperfusion” here is somewhat problematical; on the other hand, without reperfusion (spontaneous or therapeutically induced) of parts of the ischemic brain tissue, the brain metabolism will not be improved, and the ultimate objective of our therapeutic efforts is not improved cerebral blood flow (luxury perfusion, nonnutritional flow) but rather improved brain metabolism. Despite sufficient optimization of the rheological properties in the treatment group compared with the control group, we were unable to demonstrate any effect on cerebral blood flow or metabolism on \( ^{99m} \text{Tc-ECD} \) SPECT. There were no differences between the 2 groups either in the acute phase 6 to 8 hours after therapy or after the end of treatment on day 5. This cannot be due to a lack of sensitivity on the part of SPECT because we have distinctly shown that even with small numbers of patients, those with early reperfusion (within 6 to 8 hours after therapy) had a better functional 3-month outcome than patients without reperfusion. Hence, \( ^{99m} \text{Tc-ECD} \) SPECT appears to be a good indicator of clinical improvement in patients with ischemic stroke.

The main reason for extracorporeal rheopheresis failing to benefit cerebral blood flow and metabolism could be the large time window between the onset of symptoms and the start of treatment. The manner in which we provided extracorporeal rheopheresis was correct (rapid and sustained optimization of the hemorheology), and at the present time extracorporeal rheopheresis is one of the most or perhaps the most effective method to improve hemorheology. However, the therapeutic time window in patients with ischemic stroke is un-

| TABLE 4. Comparison of Patients With Early Reperfusion and Without Reperfusion |
|----------------------------------|----------------|----------------|
|                                 | Early Reperfusion | No Reperfusion |
| **SSS on admission, points**    | 28±10           | 30±5           |
| **SSS day 5, points**           | 32±15           | 25±14          |
| **Outcome day 90±14**           |                 | 0.3            |
| Modified Rankin Scale           | 2               | 4              |
| Modified Rankin Scale 0–1       | 6 (50%)         | 1 (8%)         |
| Barthel Index                   | 73±39           | 43±36          |
| Mortality                       | 2 (17%)         | 4 (33%)        |
| SPECT graded scale             |                 | 0.43           |
| On admission                    | 63±41           | 71±42          |
| 6–8 h after therapy            | 32±31           | 89±50          |
| Day 5                           | 39±55           | 88±51          |
known.38–40 Key animal experiment studies argue that after ischemia lasting >6 hours in conscious monkeys, there is no brain tissue left that can be saved.41,42 This hypothesis is also supported by the fact that all studies with neuroprotective drugs,43–45 thrombolysis,46,47 and hemodilution48 in the 6-hour time window had negative results in humans. This does not mean that individual patients may have a longer time window,49 although this appears to be the exception rather than the rule. It is probably no coincidence that the only positive stroke trial performed thus far had a 3-hour time window.49

In summary, extracorporeal rheopheresis resulted in a rapid and sustained optimization of hemorheology in patients with acute ischemic stroke. However, within a therapeutic time window of 12 hours after the start of symptoms, this treatment did not produce an improvement in neurological or functional outcome in comparison to the control patients. On 99mTc-ECD SPECT, a positive effect on cerebral blood flow and metabolism could not be ascertained either in the acute phase (6 to 8 hours after first rheopheresis) or after the end of therapy (6 to 8 hours after first rheopheresis) or after the end of the 3-month outcome than patients without reperfusion.99m Tc-ECD SPECT could be a useful tool for monitoring therapeutic interventions in patients with acute ischemic stroke.

Acknowledgments

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References


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