Prediction of Malignant Course in MCA Infarction by PET and Microdialysis

Christian Dohmen, MD; Bert Bosche, MD; Rudolf Graf, PhD; Frank Staub, MD; Lutz Kracht, MD; Jan Sobesky, MD; Michael Neveling, MD; Gerit Brinker, MD; Wolf-Dieter Heiss, MD

Background and Purpose—To predict malignant course in patients with large middle cerebral artery (MCA) infarction, we combined PET imaging and neuromonitoring, including microdialysis.

Methods—Thirty-four patients with stroke of >50% of the MCA territory in early cerebral CT scan were included. Probes for microdialysis and measurement of intracranial pressure and tissue oxygen pressure (PtO₂) were placed into the ipsilateral frontal lobe. PET was performed with ¹¹C-flumazenil to assess CBF and irreversible neuronal damage.

Results—PET measurements within 24 hours after stroke showed larger volumes of ischemic core (mean, 144.5 versus 62.2 cm³) and larger volumes of irreversible neuronal damage (157.9 versus 47.0 cm³) in patients with malignant course (ie, edema formation with midline shift) than in patients with benign course. Mean cerebral blood flow values within the ischemic core were significantly lower and the volume of the ischemic penumbra was smaller in the malignant than in the benign group. In patients with malignant course, cerebral perfusion pressure dropped to <50 to 60 mm Hg 22 to 72 hours (mean, 52.0 hours) after onset of symptoms; subsequently, PtO₂ dropped and glutamate increased, indicating secondary ischemia. Maximal changes in the monitored variables reached significant levels for glutamate, aspartate, GABA, glycerol, lactate-to-pyruvate ratio, hypoxanthine, intracranial pressure, cerebral perfusion pressure, and PtO₂.

Conclusions—PET allowed prediction of malignant MCA infarction within the time window suggested for hemicraniectomy. Neurormonitoring helped to classify the clinical courses by characterizing pathophysiological sequelae of malignant edema formation. In contrast to PET, however, it did not predict fatal outcome early enough for successful implementation of invasive therapies. (Stroke. 2003;34:2152-2158.)

Key Words: craniectomy • excitatory amino acids • microdialysis • stroke, ischemic • tomography, emission computed

Malignant brain infarcts resulting from space-occupying brain edema after ischemic stroke in the middle cerebral artery (MCA) territory carry a risk of mortality of ~80% under conservative treatment. Therefore, invasive strategies such as decompressive hemicraniectomy or induced hypothermia might be justified and have been shown to be effective in preliminary studies. Selection of patients who might benefit from these interventions and determination of the time point when the intervention must be performed to prevent large lesions not compatible with acceptable outcome require reliable assessment of irreversible ischemic damage and continuous recordings of pathophysiological markers in the affected territory. Various imaging modalities such as CT, single photon emission CT, and diffusion-weighted MRI (DWI) have been used to identify patients at risk of malignant infarction, but they all yield information on the state of the brain only at a certain time point. Because patients usually cannot be scanned sequentially and thus the time course of pathophysiological changes cannot be traced, additional continuous monitoring of physiological variables in the tissue is necessary. This can be achieved by microdialysis, which was successfully applied for monitoring the course in patients with subarachnoid hemorrhage and ischemic stroke. In the present study, PET of ¹¹C-flumazenil (FMZ) was used to identify irreversible ischemic damage because this tracer as a marker of neuronal integrity was shown to be highly predictive of the extent of the final infarct and can be used to assess cerebral perfusion. PET studies were combined with multimodal neuromonitoring to continuously follow regional changes in several physiological variables and concentration of various biochemical substrates in the extracellular space of patients with large MCA infarctions. The aim of this study was to identify predictors of malignant course and to determine the time point of critical deterioration from the course of pathophysiological markers.

Patients and Methods
This prospective study was approved by the ethics Committee of the medical faculty of the University of Cologne (approval number...
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Oxygen pressure (PtO2), and mean arterial blood pressure and arterial

high-performance liquid chromatography system. ICP, partial tissue

concentrations of glutamate, lactate, pyruvate, and glycerol with the

NaCl, 2.7 mmol/L KCl, 1.2 mmol/L CaCl2, and 0.85 mmol/L MgCl2.

EXACT HR scanner (Siemens CTI).11 PET analysis was performed

PET studies were performed in 18 of the 34 patients on an ECAT

Neuromonitoring

A microdialysis probe (CMA 70 custom probe), an intracranial

pressure (ICP) measuring device (Codman) and an oxygen sensing

probe (Licox) were inserted into the frontal lobe of the infarcted

hemisphere (34 patients). The microdialysis probe was perfused at a

rate of 0.3 μL/min with a sterile solution containing 147 mmol/L

NaCl, 2.7 mmol/L KCl, 1.2 mmol/L CaCl2, and 0.85 mmol/L MgCl2.

Samples were immediately analyzed at bedside for extracellular

concentrations of glutamate, lactate, pyruvate, and glycerol with the

CMA 600 Microdialysis Analyzer. Samples were further analyzed

posthoc for several other amino acids and for purine catabolites on a

high-performance liquid chromatography system. ICP, partial tissue

oxygen pressure (PtO2), and mean arterial blood pressure and arterial

oxygen saturation were continuously monitored. All data were added

to the database of the mainframe computer, which also was used to

analyze the microdialysis results. Neuromonitoring data from pa-

tients who underwent hemicraniectomy were excluded from data

analysis because the decompressive effect of this operation might

alter the course of the various parameters and thereby impair

comparability between patients with and without hemicraniectomy.

PET studies were performed in 18 of the 34 patients on an ECAT

EXACT HR scanner (Siemens CTI).11 PET analysis was performed by a researcher blinded to clinical data. Twenty microliters (740

MBq) FMZ was injected intravenously, and the distribution and accumulation of this tracer were followed for 60 minutes by serial

scanning. Early tracer distribution within 2 minutes after injection

allows measurement of regional cerebral blood flow (CBF). Diag-
nostic thresholds for definition of ischemic core and penumbra

regions were defined as follows.12 Reduction in ipsilateral FMZ

distribution <50% of the average distribution within the contralat-
eral hemisphere has been shown to correspond to a CBF of <14 mL

to a CBF of 14 to 20 mL·100 g−1·min−1, which is thought to be a hypoperfusional state, when the tissue is not yet irreversibly

damaged and potentially salvageable, if reperfusion can be achieved (penumbra).

FMZ uptake at steady state reflects binding to central benzodiaz-

epine receptors and is a reliable marker of neuronal integrity. As an

indicator of irreversible ischemic tissue damage, an FMZ uptake

threshold of 3.4 times the mean value of white matter was used.13 In

all patients treated with hemicraniectomy, PET scans were per-

formed before operation, so PET data from these patients were

included in the analysis.

Statistical Analysis

All results are expressed as mean±SD. Spearman’s correlation

coefficient was used to compare various variables with patient

outcome. Comparisons between patient groups were analyzed by

Student’s t test for quantitative variables and by the χ2 test for
categorical variables with significance levels of P<0.05 and

P<0.01. To define a threshold (cutoff value) with optimal diagnostic

accuracy for differentiation among groups, we determined the

receiver-operating characteristic curve (ROC) and fitted a 45° line on

that curve. If sensitivity (ordinate) is plotted versus 1−specificity

(abscissa), the best threshold is the point on the ROC that lies on a

45° line closest to the point (0.1) of the ROC plot. Statistical analysis

was performed with a commercial software package (SPSS for

Windows, version 10.0, SPSS UK).

Results

Patient Data

Of the 34 patients with hypoattenuation covering >50% of the MCA territory in early (<12 hour) CT, 17 suffered malignant course and developed space-occupying brain swelling. Eleven patients with malignant course were treated conservatively: 10 died as a result of transtentorial herniation, and 1 survived with severe neurological defects. The rema-
in 6 patients with malignant course underwent hemicrani-
tomy. The 17 patients with benign course did not develop malignant brain swelling and survived with mild to moderate handicap; 3 of these patients died because of nonneurological reasons. Of the 34 patients, 15 were treated with intravenous thrombolytic therapy: 8 developed benign and 7 developed malignant course. Space-occupying bleeding occurred in 0 of the 34 patients. In 5 patients (3 with malignant course, 2 with benign course), a slight hemorrhagic imbibition was ob-
erved; 2 of them had received thrombolytic therapy, but the

other 3 had not. From various clinical parameters, only

NIHSS after 24 hours and mRS after 3 months showed

significant differences between the 2 groups, with higher

values in the malignant group (Table 1).

Positron Emission Tomography

To exemplify PET and neuromonitoring studies, data sets from a patient with benign and a patient with malignant course are given in Figure 1.

PET measurements were performed within 3 to 24 hours

(total mean, 17.2 hours; benign group, 17.5 hours; malign-

ant group, 16.9 hours; P=NS) after onset of clinical

symptoms. Table 1 shows the summarized data of patients

who received PET with malignant course (n=8) and

patients with benign course (n=10). The volume of the ischemic core region (CBF values <50% of the mean of the unaffected hemisphere) was larger in the malignant

group (144.5 cm3) than in the benign group (62.2 cm3).
Additionally, CBF within the core region was compared with the mean of the unaffected hemisphere. This analysis revealed that CBF was decreased to 21.5% in the malignant group and only to 34.7% in the benign group \( (P<0.01) \). Finally, the volume of irreversible neuronal damage assessed by FMZ binding \( (\text{FDG-PET}) \) was significantly larger in the malignant \( (157.9 \text{ cm}^3) \) than in the benign \( (47.0 \text{ cm}^3, P<0.01) \) group. The penumbra zone, defined by flow reduction to 50% to 70% of the contralateral mean and by preserved FMZ binding, was smaller in the malignant than in the benign group \( (42.6 \text{ cm}^3) \).

The volume of irreversible neuronal damage, volume of ischemic core, and mean CBF within the core region correlated significantly with the clinical outcome of the patients \( (\text{mRS after 3 months}) \), whereas the correlation between the volume of penumbra with the \text{mRS} was not significant \( (P=0.05) \). For prediction of malignant infarction, a cutoff value for irreversible neuronal damage that amounted to 95.0 \text{ cm}^3 was determined; for the ischemic core region, a cutoff value of 105.0 \text{ cm}^3 was assessed. For mean CBF within the hypoperfused tissue, a value of 25.5% was defined \( (\text{see Table 3}) \). In the patients who died as a result of massive brain edema, PET scans were performed 54.2 hours \( (\text{mean, 20 to 81 hours}) \) before patients showed clinical signs of brain death.

**Table 1. Patient Data**

<table>
<thead>
<tr>
<th></th>
<th>Benign ( n=17 )</th>
<th>Malignant ( n=17 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age, y</td>
<td>61.3±9.5</td>
<td>55.1±11.6</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, M/F (%)</td>
<td>9/8 (53/47)</td>
<td>11/6 (65/35)</td>
<td>NS</td>
</tr>
<tr>
<td>Hemisphere, right/left (%)</td>
<td>9/8 (53/47)</td>
<td>9/8 (53/47)</td>
<td>NS</td>
</tr>
<tr>
<td>NIHSS on admission</td>
<td>18.6±4.5</td>
<td>19.7±6.1</td>
<td>NS</td>
</tr>
<tr>
<td>NIHSS 24 h after admission</td>
<td>20.1±4.3</td>
<td>26.4±8.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Leucocytes on admission, ( \text{n/μL} )</td>
<td>10 351±3 556</td>
<td>9865±3704</td>
<td>NS</td>
</tr>
<tr>
<td>Temperature on admission, °C</td>
<td>36.7±0.5</td>
<td>36.8±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Maximum temperature in first 24 h, °C</td>
<td>37.4±0.6</td>
<td>37.7±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial blood pressure on admission, mm Hg</td>
<td>125.1±13.8</td>
<td>124.4±25.8</td>
<td>NS</td>
</tr>
<tr>
<td>mRS 3 mo after admission</td>
<td>4.1±1.3</td>
<td>5.6±0.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>CBF and neuronal damage in FMZ-PET</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume of irreversible neuronal damage, ( \text{cm}^3 )</td>
<td>47.0±46.9</td>
<td>157.9±37.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Volume of critically hypoperfused tissue (core), ( \text{cm}^3 )</td>
<td>62.2±37.2</td>
<td>144.5±27.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean CBF within ischemic core, %</td>
<td>34.7±6.6</td>
<td>21.5±3.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Volume of moderately hypoperfused tissue (penumbra), ( \text{cm}^3 )</td>
<td>58.0±14.4</td>
<td>42.6±14.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SD when appropriate.

**Figure 1.** In benign infarcts, volume of severe hypoperfusion and neuronal damage, ie, reduced FMZ binding, were smaller than in patients with malignant course. Neuromonitoring did not reveal significant deflections of variables, whereas in malignant patients, substrate concentrations and intracranial pressure rose progressively.
Neuromonitoring was started within 12 to 34 hours after stroke onset. Patients with benign course of ischemia generally showed low and stable values of the various parameters throughout the measurement, whereas in patients with malignant course, marked changes in substrate concentrations were detected. Although the time points of maximal deflections varied in patients with malignant infarction, peak values of the various parameters were reached in all patients only in the later course of ischemia, ie, days after stroke onset (mean, 74.2 to 100.6 hours; see Figure 2). The impact of alterations assessed by continuous neuromonitoring on the clinical course was analyzed by correlating the peak values (maxima for extracellular substrates and ICP and minima for cerebral perfusion pressure [CPP] and PtO$_2$) of the various variables throughout the measurement to patient outcome (Table 2). Significant correlations between outcome and peak values were observed for the transmitter amino acids glutamate, aspartate, and GABA; for glycerol as an indicator for membrane degradation; for the energy metabolite lactate-to-pyruvate ratio and hypoxanthine; and for ICP, CPP, and PtO$_2$.

### Table 2. Correlation Between Outcome and PET and Neuromonitoring

<table>
<thead>
<tr>
<th>Parameter</th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET and mRS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume of irreversible neuronal damage</td>
<td>0.75</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Volume of ischemic core</td>
<td>0.76</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean CBF within the ischemic core</td>
<td>-0.63</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Volume of penumbra</td>
<td>-0.24</td>
<td>NS</td>
</tr>
<tr>
<td>Neuromonitoring and mRS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glutamate</td>
<td>0.61</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Aspartate</td>
<td>0.62</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>GABA</td>
<td>0.58</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Glycerol</td>
<td>0.56</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Lactate/pyruvate ratio</td>
<td>0.67</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypoxanthine</td>
<td>0.60</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ICP</td>
<td>0.85</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CPP</td>
<td>-0.82</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PtO$_2$</td>
<td>-0.83</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

### Table 3. Identification of Malignant MCA Infarction

<table>
<thead>
<tr>
<th>Identification Factor</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Positive Predictive Value, %</th>
<th>Negative Predictive Value, %</th>
<th>$\chi^2$</th>
<th>P</th>
<th>Likelihood Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuronal damage $&gt;95$ cm$^3$</td>
<td>99</td>
<td>77</td>
<td>77</td>
<td>99</td>
<td>11.52</td>
<td>&lt;0.001</td>
<td>11.52</td>
</tr>
<tr>
<td>Ischemic core $&gt;105$ cm$^3$</td>
<td>99</td>
<td>68</td>
<td>71</td>
<td>99</td>
<td>9.16</td>
<td>&lt;0.01</td>
<td>11.84</td>
</tr>
<tr>
<td>Mean CBF within core $&lt;25.5$%</td>
<td>99</td>
<td>86</td>
<td>85</td>
<td>99</td>
<td>14.40</td>
<td>&lt;0.001</td>
<td>18.45</td>
</tr>
<tr>
<td>Neuromonitoring parameters</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Glutamate $&gt;46.0$ μmol/L</td>
<td>70</td>
<td>100</td>
<td>99</td>
<td>79</td>
<td>14.18</td>
<td>&lt;0.001</td>
<td>17.66</td>
</tr>
<tr>
<td>Aspartate $&gt;4.2$ μmol/L</td>
<td>82</td>
<td>92</td>
<td>90</td>
<td>86</td>
<td>13.46</td>
<td>&lt;0.001</td>
<td>15.12</td>
</tr>
<tr>
<td>GABA $&gt;9.0$ μmol/L</td>
<td>54</td>
<td>100</td>
<td>99</td>
<td>71</td>
<td>9.45</td>
<td>&lt;0.01</td>
<td>11.83</td>
</tr>
<tr>
<td>Glycerol $&gt;543$ μmol/L</td>
<td>100</td>
<td>88</td>
<td>88</td>
<td>100</td>
<td>18.33</td>
<td>&lt;0.0001</td>
<td>23.61</td>
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<tr>
<td>Lactate/pyruvate ratio $&gt;50.0$</td>
<td>77</td>
<td>100</td>
<td>99</td>
<td>77</td>
<td>15.95</td>
<td>&lt;0.0001</td>
<td>19.72</td>
</tr>
<tr>
<td>Hypoxanthine $&gt;39$ μmol/L</td>
<td>63</td>
<td>100</td>
<td>99</td>
<td>75</td>
<td>11.68</td>
<td>&lt;0.001</td>
<td>14.55</td>
</tr>
<tr>
<td>ICP $&gt;26.6$ mm Hg</td>
<td>96</td>
<td>100</td>
<td>100</td>
<td>96</td>
<td>24.00</td>
<td>&lt;0.00001</td>
<td>33.10</td>
</tr>
<tr>
<td>PtO$_2$ $&gt;10.5$ mm Hg</td>
<td>94</td>
<td>100</td>
<td>99</td>
<td>95</td>
<td>18.00</td>
<td>&lt;0.00001</td>
<td>24.73</td>
</tr>
<tr>
<td>CPP $&gt;56$ mm Hg</td>
<td>95</td>
<td>100</td>
<td>100</td>
<td>96</td>
<td>22.00</td>
<td>&lt;0.000001</td>
<td>30.31</td>
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<tr>
<td>Clinical parameters</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS after 24 h $&gt;20.5$</td>
<td>55</td>
<td>62</td>
<td>54</td>
<td>62</td>
<td>0.62</td>
<td>NS</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Figure 2. Peak values (mean±SD) of interstitial metabolites and intracranial pressure and minimal values of cerebral perfusion pressure and PtO$_2$ for patients with malignant vs benign clinical course after infarction. In patients with malignant course, significantly higher values were observed for all microdialysis parameters and ICP; significantly lower values were seen for PtO$_2$ and CPP. Time point of mean peak value of patients with malignant course is indicated below name of the parameter (hours after stroke). *$P<0.05$, #$P<0.01$. 

Dohmen et al Predicting Malignant Course in MCA Infarction 2155

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When CPP fell below the critical threshold of 50 to 60 mm Hg, extracellular concentrations of excitatory amino acids, GABA, and energy metabolites started to increase. At this point, PtO2 decreased and fell to <10 mm Hg. In all patients who died as a result of transtentorial herniation, the mean time interval between drop of CPP to <60 mm Hg and clinical signs of brain death was 10.3 hours (range, 2 to 19 hours).

**Discussion**

**Prediction of Malignant MCA Infarction by Clinical Data**

Several retrospective case-control studies have been conducted to determine clinical predictors of neurological death in patients with large MCA infarction. As clinical factors, patient’s age, NIHSS on admission, white blood cell count, fever, blood pressure within the first 12 hours, and nausea/vomiting have been suggested to be valuable for differentiating between patients with and without massive edema formation. In our study, of all clinical parameters, only differences in NIHSS after 24 hours and mRS after 3 months reached statistical significance. This might be explained in part by the fact that in previous studies, values on admission have often been taken only within the first 24 to 48 hours, whereas in our study, these data were taken within the first 12 hours. In addition, measurements of blood pressure after admission are, for example, often influenced by blood pressure–modulating therapies. Likewise, nausea/vomiting after stroke often cannot be evaluated because patients are sedated, intubated, and provided with a gavage. Consequently, we excluded the parameters blood pressure after admission and nausea/vomiting from further analysis. Even though the number of patients included in our study is limited, it seems justified to conclude from our results that relying on clinical factors alone to identify patients with impending brain edema is insufficient.

**Prediction of Malignant MCA Infarction by FMZ-PET**

The only radiological predictor that was confirmed in all previous studies was a hypodensity extending over >50% of the MCA territory in early CT. In our prospective study, we used this CT finding as the main inclusion criterion. Our finding that only 50% of included patients with hypodensity >50% developed space-occupying brain swelling implies that this criterion alone may not sufficiently predict fatal brain edema. In our study, the extent of irreversibly damaged neuronal tissue and the extent of the ischemic core region determined by FMZ-PET were shown to be significantly larger in patients with malignant than in patients with benign course. Thus, FMZ-PET allows reliable prediction of malignant MCA infarction within the time window in which hemicraniectomy has been shown to be most effective, ie, within 24 hours after stroke. Recently, Oppenheim et al have...
used DWI to study patients with impending malignant MCA infarction. Regarding DWI lesion volumes, they found a mean DWI volume of 244 cm³ in patients with malignant MCA infarction and a cutoff value of >145 cm³ to predict massive brain edema within the first 14 hours after stroke. In contrast to DWI, which represents irreversibly damaged tissue by measurement of impaired diffusion, FMZ-PET allows measurement of irreversible tissue damage by direct binding of FMZ to neuronal benzodiazepine receptors. We identified a mean volume of neuronal damage, ie, reduced FMZ binding, of 158 cm³ and a cutoff value of 95 cm³ in patients with malignant course. That volumes of reduced FMZ binding are smaller than DWI lesion volumes found by Oppenheim et al might be partly explained by the fact that FMZ-PET predominantly marks damage in cortical areas.

Furthermore, we found the ischemic core to be significantly larger and ischemia to be more severe within this critically hypoperfused tissue. For prediction of space-occupying brain edema, a cutoff value for mean CBF within the hypoperfused tissue of 25.5% of the contralateral hemisphere was found. This value correlates to a CBF of 8 to 14 mL · 100 g⁻¹ · min⁻¹ and indicates that a large portion of the hypoperfused tissue is presumably already irreversibly damaged. This assumption gains further support from the finding that the volume of ischemic penumbra was smaller in patients who finally developed malignant brain edema. This result can be explained by the fact that patients with large MCA infarction have little penumbra, ie, hypoperfused but still viable tissue, that could be salvaged by reperfusion therapy. For those patients, additional therapeutic options like early hemicraniectomy should be considered.

For irreversible neuronal damage and for ischemic core region, cutoff values of 95 and 105 cm³, respectively, could be identified with high sensitivity but only moderate specificity; these values distinguished patients with eventually malignant from those with benign course. These values might be affected by data obtained in a single patient who was hemicraniectomized because of signs of brain swelling in early CT scan and was therefore classified as malignant. Compared with the other patients, however, this patient showed relatively small volumes of irreversible damage and critical hypoperfusion and was perhaps misclassified as having malignant infarction.

**Prediction of Malignant MCA Infarction by Multimodal Neuromonitoring**

Microdialysis has been successfully applied to trace biochemical alterations in the pathophysiology of various clinical entities such as subarachnoid hemorrhage, trauma, and stroke. Although imaging modalities yield information on the pathological state of the whole brain only for the time point of the scan, neuromonitoring with microdialysis, ICP, and PtO₂ allows continuous, longitudinal monitoring. It is, however, restricted to a small volume of brain tissue. Berger et al have reported an anecdotal case in which microdialysis measurement in the noninfarcted tissue of a patient with a large MCA infarction showed early alterations of extracellular substrate concentrations that might predict a malignant course. We used standardized implantation of the probes into the frontal peri-infarct region. Implantation of the probes and the monitoring itself caused no harm to the patients, and no infection or symptomatic bleeding occurred.

Results of the multimodal neuromonitoring revealed marked changes in the dynamics of the different substances in accordance with the clinical course, size of infarction, and local brain edema. Peak values reached throughout the measuring period correlated to clinical outcome and showed significant differences in the various parameters between patients with malignant and benign course. However, in all patients with malignant course, peak values were reached only days after stroke. In a subset of patients with malignant course, it was possible to continue multimodal neuromonitoring during the period of secondary ischemia characterized by a drop of CPP to ≤50 to 60 mm Hg. In these patients (Figure 3), rapid concentration changes occurred when they reached the critical state of infarction, indicating deterioration with secondary ischemia of the tissue being monitored. The pathophysiological cascade finally leading to enlargement of infarction resulting from space-occupying brain edema could clearly be monitored in these patients. The initially infarcted tissue begins to swell because of an increase in net water content in the infarcted tissue (hypodensity in the CT scan), and the rising ICP then leads to a decrease in CPP. When CPP falls under a critical threshold (≤50 to 60 mm Hg), PtO₂ drops to <10 mm Hg, which is known to be a threshold value for hypoxic tissue. At this time point, a rise in the lactate-to-pyruvate ratio and hypoxanthine is detected, indicating a change from aerobic to anaerobic metabolism and increased breakdown of ATP under ischemic stress. Subsequently, concentrations of excitatory amino acids and GABA increase. Infarction of this primary nonischemic tissue can be documented in late CT of patients with secondary ischemia and is presumably part of the vicious circle finally leading to transtentorial herniation. Concerning the critical threshold of CPP, we found consistency with results of an experimental study from this laboratory in which secondary ischemia with an increase in extracellular glutamate was measured in an animal model of malignant MCA infarction when the CPP fell to <50 to 60 mm Hg. Therefore, we recommend that the CPP should be held well above 60 mm Hg at all times to avoid deleterious expansion of ischemia in patients with impending brain edema. From these results, we conclude that multimodal neuromonitoring in the peri-infarct region, especially CPP and PtO₂, could indicate the critical state of ischemia, ie, herniation by brain edema. At this time point, however, effective implementation of invasive therapies like hemicraniectomy might be too late.

It has to remain a goal for further studies to evaluate the prognostic value of measurements in other compartments of the ischemic territory, eg, in the core, and of other parameters not yet determined.

**Conclusions**

This complex study combining PET with continuous neuromonitoring revealed significant differences in the extent of critical CBF reduction, early neuronal damage, extracellular substrate concentrations, ICP, and PtO₂ values between patients who developed malignant brain edema and those who
did not. Early prediction of malignant infarction was possible with FMZ-PET, whereas multimodal neuromonitoring identified the critical stage of deterioration in the later course of ischemia, namely expansion of ischemia and transtentorial herniation. The results of our study aid in the selection of patients who might benefit from invasive therapeutic strategies and characterization of the pathophysiology of malignant MCA infarction.

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Christian Dohmen, Bert Bosche, Rudolf Graf, Frank Staub, Lutz Kracht, Jan Sobesky, Michael Neveling, Gerit Brinker and Wolf-Dieter Heiss

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