Increased Blood–Brain Barrier Permeability on Perfusion CT Might Predict Malignant Middle Cerebral Artery Infarction

Hesna Bektas, MD; Tzu-Ching Wu, MD; Mallikarjunarao Kasam, PhD; Nusrat Harun, MS; Clark W. Sitton, MD; James C. Grotta, MD; Sean I. Savitz, MD

Background and Purpose—Perfusion CT has been used to assess the extent of blood–brain barrier breakdown. The purpose of this study was to determine the predictive value of blood–brain barrier permeability measured using perfusion CT for development of malignant middle cerebral artery infarction requiring hemicraniectomy (HC).

Methods—We retrospectively identified patients from our stroke registry who had middle cerebral artery infarction and were evaluated with admission perfusion CT. Blood–brain barrier permeability and cerebral blood volume maps were generated and infarct volumes calculated. Clinical and radiographic characteristics were compared between those who underwent HC versus those who did not undergo HC.

Results—One hundred twenty-two patients (12 HC, 110 no HC) were identified. Twelve patients who underwent HC had developed edema, midline shift, or infarct expansion. Infarct permeability area, infarct cerebral blood volume area, and infarct volumes were significantly different \((P<0.018, P<0.0211, P<0.0001, P<0.0014)\) between HC and no HC groups. Age \((P=0.03)\) and admission National Institutes of Health Stroke Scale \((P=0.0029)\) were found to be independent predictors for HC. Using logistic regression modeling, there was an association between increased infarct permeability area and HC. The OR for HC based on a 5-, 10-, 15-, or 20-cm\(^2\) increase in infarct permeability area were 1.179, 1.390, 1.638, or 1.932, respectively (95% CI, 1.035 to 1.343, 1.071 to 1.804, 1.108 to 2.423, 1.146 to 3.255, respectively).

Conclusion—Increased infarct permeability area is associated with an increased likelihood for undergoing HC. Because early HC for malignant middle cerebral artery infarction has been associated with better outcomes, the infarct permeability area on admission perfusion CT might be a useful tool to predict malignant middle cerebral artery infarction and need for HC. (Stroke. 2010;41:2539-2544.)

Key Words: acute stroke • blood–brain barrier • diffusion-weighted imaging • hemicraniectomy • malignant middle cerebral infarction • neuroradiology • perfusion CT • treatment

Approximately 10% to 15% of all patients with cerebral infarction in the territory of the middle cerebral artery (MCA) have progressive clinical deterioration because of increasing brain swelling, raised intracranial pressure, and brain herniation. This patient population constitutes a particularly difficult challenge for clinicians charged with their care.1–3 Because of the limitations of medical therapies, decompressive surgery is an option for patients with neurological deterioration due to large hemispheric infarction and edema. The rationale of this therapy is to prevent brain tissue shifts and to normalize intracranial pressure and thereby preserve cerebral blood flow and prevent secondary damage.4 Hemicraniectomy (HC) for malignant middle cerebral artery infarctions (MMA) has been shown to be an effective treatment.5 Currently, clinical data and early cranial tomography does not reliably identify patients who will develop MMA. Prognostic criteria that might permit early identification of patients at risk for such “malignant” infarction are important.6–8

Perfusion CT (PCT) is a modern imaging technique that has been proposed for evaluating patients with acute stroke at the time of their emergent evaluation. PCT involves the sequential acquisition of CT images performed in cine mode during the intravenous administration of iodinated contrast material and has been reported to allow for accurate quantitative assessment of cerebral blood flow and cerebral blood volume (CBV).8 It also has been validated in determining final infarct volumes and measuring potentially salvageable tissue using different PCT maps.10 By extending the PCT acquisition time window, blood–brain barrier permeability...
(BBBP) can also be obtained. PCT techniques for measuring BBBP have been shown to be achievable in tumor models in animals and in a small human series, but only recently has it been applied to acute stroke imaging. The aim of this retrospective study was to determine whether permeability maps, generated from admission PCT, can be used to predict MMCA. We hypothesized that patients with an increased area of permeability defect would be at higher risk for development of MMCA.

Methods
We retrospectively reviewed our registry from August 2007 to August 2009 and identified 268 consecutive patients diagnosed with MCA infarctions (18 patients in the HC group and 250 patients in nonhemicraniectomy [NHC] group). We included in our analysis patients who underwent PCT on admission with interpretable permeability maps. Two patients in the HC and 31 patients in NHC group had uninterpretable PCT maps. Three patients in the HC and 76 patients in the NHC groups did not have PCT. Patients who had their care withdrawn were also excluded from the analysis. In total, 122 patients fit our criteria: 12 underwent HC and 110 in the NHC group. Demographic characteristics and baseline clinical information including admission National Institutes of Health Stroke Scale (NIHSS), admission glucose level, HbA1c, lipids, the timing of MRI acquisition, and PCT were extracted from the medical records. Clinical, laboratory, and radiographic characteristics were analyzed between the 2 groups.

Calculation of Infarct Volumes
All MRI scans were performed before decompression in the HC group. One of the investigators was blinded to clinical outcomes and independently reviewed all the diffusion-weighted images (DWIs) to verify infarct volumes. Infarct volumes were measured by hand-drawn regions of interest around each area of infarct in every slice separately. The regions of interest area was calculated automatically by the Picture Archiving and Communication Systems software (General Electric Centricity workstation) and then multiplied by the slice thickness (5 mm for DWI). Seven patients (58.3%) in the HC group and 85 patients (77.3%) in the NHC group had DWI.

Calculation of Permeability and CBV Volume
Permeability color maps was retrospectively generated from PCT data using a modified Patlak method. PCT was performed on a Siemens Somatom Sensation 40 scanner. After intravenous administration of 40 mL iodinated contrast at 8 mL/s by a power injector into an antecubital vein (Omnipaque, 350/40 mL), images were acquired without delay. PCT imaging parameters were 80 kVp, 270 mAs, and 1.2-mm section collimation. Slice thickness was 9.6-mm acquired 3 slices at a time for 75 seconds. The modified Patlak model (in Siemens Syngo Neuro PCT) calculates vascular permeability (PS) with CT enhancement values after the peak contrast enhancement has been reached and using a built-in delay correction algo-
This allows estimation of PS during the end of the first passage of contrast but avoids erroneous elevation of PS values secondary to delayed arrival of contrast, which would occur in a standard application of the Patlak model to PCT data in the setting of acute cerebral ischemia. From the PCT data, permeability maps were calculated using Syngo Neuro PCT software, which sets the threshold for generating the permeability maps at 0.5 mL/100 mL/min. We defined the perfusion abnormality as the region analyzed on the permeability maps, IP as the weighted mean of the permeability value, and IP\textsubscript{area} as the area of the region that had perfusion abnormality. Each permeability map was analyzed by demarcating trace lines around the area of perfusion abnormality on each of the 3 slices. IP and IP\textsubscript{area} values were measured by hand-drawn regions of interest in every slice separately. The weighted mean of IP and IP\textsubscript{area} of the 3 slices was calculated, respectively, and used for statistical analysis. Contralateral nonischemic hemisphere was used as a control.

Using the Siemens Syngo Neuro software, CBV was calculated along with cerebral blood flow using the maximal slope model, which has been shown to yield lesion volumes that are similar to delay-insensitive deconvolution techniques. The hypoperfused areas on CBV maps were defined as volume abnormality. The infarct core was outlined on CBV maps as a severely hypoperfused area displayed by 2 colors in the color bar (eg, purple and blue). The CBV threshold was defined at 2.0 mL/100 g. Each CBV map was analyzed by demarcating trace lines around the area of volume abnormality on each of the 3 slices by hand-drawn regions of interest. The area of volume abnormality was defined as CBV\textsubscript{area}. The weighted mean of CBV and CBV\textsubscript{area} was calculated in each of the 3 slices, respectively, and used for statistical analysis. Representative images of CBV and permeability are shown in Figure 1 from a patient who developed malignant infarction and underwent HC.

### Statistical Analysis

Means with SDs or medians for continuous variables and proportions for categorical variables were used. The differences were assessed using t tests, \( \chi^2 \) tests, Fisher exact test, or Mann-Whitney U test. A significance level of 0.05 was used to assess statistical difference. We used multivariate analysis using logistic regression to obtain ORs to determine associations controlling for potential confounders. The statistical analysis was performed using SAS 9.2.

### Results

#### Patients

We included 122 patients in total, 12 HC and 110 NHC. Of the baseline characteristics analyzed, mean age (56.08±13.20 versus 65.40±13.66 years; \( P<0.03 \)) was statistically different between the HC and NHC groups. Patients in the HC group were significantly younger than the NHC group. Other baseline characteristics such as gender, race, and risk factors were not statistically different between the 2 groups (Table 1). Laboratory parameters (mean serum glucose at admission, HbA1c level, serum total cholesterol level, triglyceride, high-density lipoprotein, low-density lipoprotein) assessed at baseline were not significantly different between HC and NHC groups.

#### Clinical Factors

Baseline stroke severity, as measured by median NIHSS scores, was significantly higher in the HC group than the NHC group (19 [range, 11 to 29] versus 11 [range, 0 to 40]; \( P<0.0029 \)). The mean time from stroke onset to PCT in minutes in the HC and NHC groups were 310.55±306.75 and 502.56±845.90, respectively. There was no significant difference in time to PCT scanning between 2 groups (\( P=0.19 \)).

<table>
<thead>
<tr>
<th>Age, years (mean±SD)</th>
<th>HC Group (n=12)</th>
<th>NHC Group (n=110)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>56.08±13.20</td>
<td>65.40±13.66</td>
<td>0.03*</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>( F ) test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>0.66†</td>
</tr>
<tr>
<td>Male</td>
<td>0.44‡</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Race</th>
<th>( \chi^2 ) test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>0.11‡</td>
</tr>
<tr>
<td>White</td>
<td>0.74‡</td>
</tr>
</tbody>
</table>

### Radiographic Characteristics

Mean DWI infarct volume was significantly larger in the HC group compared with the NHC group (162.20±61.20 versus 43.62±55.33 mL; \( P<0.0014 \)). Patients with infarct volumes >145 mL were more likely to receive HC (62.5% versus 37.5%; \( P<0.0001 \)).

No significant differences in IP were observed between the 2 groups (7.26±2.95 mL·min\(^{-1} \)·[100 g\(^{-1} \)] versus 8.44±7.42 mL·min\(^{-1} \)·[100 g\(^{-1} \)]; \( P=0.2950 \)). Similarly, no significant differences in mean CBV were observed between HC and NHC groups (13.72±12.89 mL·[100 g\(^{-1} \)] versus 16.55±12.15 mL·[100 g\(^{-1} \)]; \( P=0.4487 \); Table 2).

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>( \chi^2 ) test</th>
<th>( \chi^2 ) test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>0.71†</td>
<td>0.7680</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.72‡</td>
<td>0.72‡</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>0.72‡</td>
<td>0.72‡</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.22‡</td>
<td>0.22‡</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>0.74‡</td>
<td>0.74‡</td>
</tr>
</tbody>
</table>

Seven (58.3%) patients in the HC group and 85 (77.3%) patients in the NHC group had DWI (\( P<0.0035 \)). Onset to acquired DWIs was not statistically different (877.6±712.7 versus 975.5±709.4 minutes, \( P=0.7680 \); Table 2).

<table>
<thead>
<tr>
<th>Clinical Factors</th>
<th>HC Group (n=12)</th>
<th>NHC Group (n=110)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission NIHSS median (minimum to maximum)</td>
<td>19 (11–29)</td>
<td>11 (0–40)</td>
<td>0.0029†</td>
</tr>
<tr>
<td>Onset to PCT, minutes (mean±SD)</td>
<td>310.55±306.75</td>
<td>502.56±845.90</td>
<td>0.19*</td>
</tr>
<tr>
<td>Onset to DWI, minutes (mean±SD)</td>
<td>877.6±712.7</td>
<td>975.5±709.4</td>
<td>0.76*</td>
</tr>
<tr>
<td>Intravenous tissue plasminogen activator given (%)</td>
<td>4 (33.33)</td>
<td>60 (54.55)</td>
<td>0.22†</td>
</tr>
</tbody>
</table>

*\( t \)-test.
†Two-sample test.
‡Fisher exact test.
(61.97±27.10 vs 41.485±32.270; P<0.018). We used a logistic regression model to determine whether IParea is associated with the probability of having a HC, controlling for potential confounders. We found that the odds of receiving a HC was higher for patients with larger IParea (OR, 1.042; 1.019 to 1.066; P=0.0016) but not with CBV lesion volume (OR, 0.976 [0.916 to 1.040]; P=0.4513). However, when controlling for the DWI volume, there was no association between receiving HC and IParea (OR, 1.008 [0.975 to 1.041]; P=0.6391). There was no correlation between DWI volume and IParea (P=0.5219). We also did not find a correlation between IParea and admission NIHSS (P=0.0817), HbA1c levels (P=0.9072), or admission glucose levels. (P=0.6542).

**Discussion**

Progressive deterioration of clinical status due to massive hemispheric edema occurs in 10% of patients and is described as the “MMCA.” Ischemic edema occurs within hours after stroke onset and is initially cytotoxic characterized by intracellular water accumulation, and later vasogenic, in which water moves across the blood–brain barrier (BBB) into the extracellular interstitial space. The disruption of the BBB can be demonstrated as early as 20 minutes after brain ischemia in rats.18,19

Over the past 15 years, several studies have shown that decompressive surgery is a possible treatment strategy for increased intracranial pressure after severe hemispheric stroke and can reduce the mortality to <50%.3,20–23 The clinical course of many patients with severe MCA stroke is predictable. Therefore, waiting for pupillary dilatation causes an unnecessary delay.24,25 However, there is little information to guide clinicians in selecting which patients are most suitable for this aggressive intervention.

The aim of this study was to define radiographic predictors of malignant MCA infarct in retrospectively evaluated patients with MCA stroke and to provide early prognostic factors that may affect treatment decisions of clinicians. Patients who underwent HC were significantly younger than the NHC group. Wijdicks and colleagues26 suggested that intracranial pressure in younger patients might rise rather quickly due to less reserve to compensate for the increase in intracranial pressure after severe hemispheric stroke.2,7,8,27 Age is an important factor for deciding to pursue surgery and clinicians focus on younger patients before signs of herniation appear such as stroke severity. Krieger et al reported that patients with malignant MCA strokes had higher NIHSS scores at admission and no single item or cluster of items in the NIHSS was a predictor of fatal brain edema than the total NIHSS score.8 Higher NIHSS scores at admission were found in our HC group as well.

DVI is increasingly being used for the early management of acute stroke.28 Oppenheim et al28 had used DVI to study patients with impending malignant MCA infarction and found a mean DVI volume of 244 cm³ in patients with malignant MCA infarction and a cutoff volume of 145 cm³ to predict massive brain edema within the first 14 hours after stroke.28 We identified a mean volume of infarct of 162.20 cm³ and a cutoff volume of 100 cm³ in the HC population. Quantitative measurement of DVI volumes is a reliable factor to decide for HC.

Other radiographic factors may play a role in determining the population at risk for subsequent fatal ischemic brain edema.3,29,30

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**Table 3. Radiographic Measurements**

<table>
<thead>
<tr>
<th>Radiographic Measurements</th>
<th>HC Group (n=12)</th>
<th>NHC Group (n=110)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>DWI infarct volumes (mean±SD), cm³</td>
<td>162.20±81.20 (n=7)</td>
<td>43.62±55.33 (n=85)</td>
<td>0.0014†</td>
</tr>
<tr>
<td>DWI infarct volumes ≥145 cm³ (%)</td>
<td>5 (83.33%)</td>
<td>1 (16.67%)</td>
<td>0.0001†</td>
</tr>
<tr>
<td>Infarct permeability</td>
<td>7.26 mL·min⁻¹·[100 g]⁻¹±2.95</td>
<td>8.44 mL·min⁻¹·[100 g]⁻¹±7.42</td>
<td>0.29*</td>
</tr>
<tr>
<td>Infarct permeability area</td>
<td>61.97 cm²±27.10</td>
<td>41.48 cm²±32.27</td>
<td>0.018‡</td>
</tr>
<tr>
<td>Contralateral permeability</td>
<td>2.80 mL·min⁻¹·[100 g]⁻¹±1.88</td>
<td>2.71 mL·min⁻¹·[100 g]⁻¹±3.11</td>
<td>0.92*</td>
</tr>
<tr>
<td>Infarct CBV</td>
<td>13.72 mL·[100 g]⁻¹±12.89</td>
<td>16.55 mL·[100 g]⁻¹±12.15</td>
<td>0.44*</td>
</tr>
<tr>
<td>Infarct CBV area</td>
<td>48.36 cm²±24.23</td>
<td>29.14 cm²±27.33</td>
<td>0.0211*</td>
</tr>
<tr>
<td>Contralateral cerebral blood volume</td>
<td>29.80 mL·[100 g]⁻¹±10.04</td>
<td>28.86 mL·[100 g]⁻¹±10.72</td>
<td>0.77*</td>
</tr>
</tbody>
</table>

*Student t test.
†χ² test.
‡Two-sample test.
swelling.\textsuperscript{8} PCT is an imaging technique currently used to evaluate patients with acute stroke at the time of their emergency evaluation.\textsuperscript{9} Dittrich et al have even reported that the blood flow and volume parameters of PCT might permit identifying patients at risk for malignant infarction.\textsuperscript{29} More recently, PCT has been used to characterize the BBBP.\textsuperscript{15,30,31} A relatively simple and frequently applied model to calculate BBBP is the Patlak model.\textsuperscript{32,33} Applying this model to PCT data\textsuperscript{15,34–36} requires using arterial and parenchymal contrast enhancement curves to calculate the rate of contrast transfer from the intravascular to the extravascular compartment, which is a measure of BBBP. Microvascular permeability (expressed as the transendothelial transfer constant or PS area product) is a metric of BBB integrity. Similar to the standard perfusion metrics, PS can also be calculated using dynamic imaging by measuring the leakage of an intravascular tracer into the extravascular (interstitial) space.\textsuperscript{33,37,38}

In the normal brain parenchyma, PS is 0 for relatively large hydrophilic molecules (such as a peripherally injected iodinated contrast agent), which reflects the tight regulation of the BBB.\textsuperscript{39–42} Evidence from animal and human studies suggests that increased permeability can occur in the first 2 to 4 hours of acute ischemia.\textsuperscript{43–45} In our study, the infarct permeability area and infarct cerebral blood volume area of the ischemic region determined by PCT were shown to be significantly larger in patients in the HC group. This result can be explained by the fact that the patients with larger infarct permeability developed malignant brain edema. Recently PCT data were also used to characterize the BBBP in an effort to predict which patients with stroke develop hemorrhagic transformation.\textsuperscript{15} Lin et al showed that elevated PS had been detectable during the hyperacute period using first-pass dynamic CT data and was predictive for hemorrhagic transformation in patients who received tissue plasminogen activator.\textsuperscript{15} Aviv et al evaluated the admission PS measurements of patients with acute stroke and reported that a PS threshold of 0.23 mL · (100 g) \textsuperscript{-1} had high sensitivity and specificity for predicting hemorrhagic transformation.\textsuperscript{46} Taken together, these studies along with our results underscore the fact that a compromise in the BBB is a necessary but not sufficient criterion for hemorrhagic transformation. If the permeability of the BBB is not large enough for blood cellular elements (red blood cells, platelets) to pass, hemorrhage will not occur, but the BBB only needs to be permeable to much smaller molecules such as albumin for water to follow it into the interstitial space and cause edema. BBB permeability maps may therefore have even more use than just predicting hemorrhage by showing which patients may develop malignant edema.

This study is limited by its retrospective design and small sample number in the HC group. There could also have been variations in the gravity of the MCA infarcts (eg, internal carotid artery infarct with involvement of the anterior cerebral artery), which may have favored HC and thus may have introduced a systematic difference between the HC and NHC groups. In addition, we found that in multivariate regression, IP\textsubscript{area} was no longer predictive of HC when controlling for DWI lesion volume. Although DWI lesion size may be more predictive for HC, MRI is not always available or feasible for all patients in the initial management period, particularly for patients with large strokes who are susceptible to malignant edema (as shown by our data in which patients with deterioration were less likely to have DWI follow-up). Thus, the BBB permeability map might be useful in predicting patients who will develop MMCA, especially in light of the result that the CBV (core) lesion area was not predictive of deterioration. Thus, the modified Patlak permeability map uniquely offers novel information over the conventional perfusion CT maps and PCT can be obtained rapidly when the patient first presents to the emergency department.

In conclusion, the IP\textsubscript{area} on admission PCT might be a useful tool to predict MMCA and need for HC. Given that studies suggest early rather than delayed HC for MMCA is associated with better outcomes,\textsuperscript{20,46,47} further prospective studies are needed to validate our findings.

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**Disclosures**

None.

**References**


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