Improved Hemodynamic Parameters in Middle Cerebral Artery Infarction After Decompressive Craniectomy

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Background and Purpose—Decompressive craniectomy (DC) reduces mortality and improves functional outcome in patients with malignant middle cerebral artery infarction. However, little is known regarding the impact of DC on cerebral hemodynamics. Therefore, our goal was to study the hemodynamic changes that may occur in patients with malignant middle cerebral artery infarction after DC and to assess their relationship with outcomes.

Methods—Twenty-seven patients with malignant middle cerebral artery infarction who were treated with DC were studied. The perfusion CT hemodynamic parameters, mean transit time, cerebral blood flow, and cerebral blood volume were evaluated preoperatively and within the first 24 hours after DC.

Results—There was a global trend toward improved cerebral hemodynamics after DC. Preoperative and postoperative absolute mean transit times were associated with mortality at 6 months, and the ratio of post- and preoperative cerebral blood flow was significantly higher in patients with favorable outcomes than those with unfavorable outcomes. Patients who underwent surgery 48 hours after stroke, those with midline brain shift >10 mm, and those who were >55 years showed no significant improvement in any perfusion CT parameters.

Conclusions—DC improves cerebral hemodynamics in patients with malignant middle cerebral artery infarction, and the level of improvement is related to outcome. However, some patients did not seem to experience any additional hemodynamic benefit, suggesting that perfusion CT may play a role as a prognostic tool in patients undergoing DC after ischemic stroke. (Stroke. 2014;45:00-00.)

Key Words: cerebral infarction • decompressive craniectomy • perfusion imaging

Malignant middle cerebral artery (MCA) infarction is used to describe the rapid neurological worsening that occurs because of the effects of a space-occupying cerebral edema secondary to a MCA territory stroke. It is a potential lethal clinical condition that has a poor outcome and mortality of ~80% without surgical treatment.1 Decompressive craniectomy (DC) is increasingly being used to avoid the harmful consequences of cerebral edema and intracranial pressure elevation in cases of malignant brain ischemia.2–4 This treatment has been consistently associated with a decrease in mortality; however, the benefits in terms of functional outcome remain uncertain. A post hoc analysis of pooled data from 3 randomized control trials showed that patients who underwent surgery <48 hours after stroke have better functional outcomes compared with those operated later.5 Therefore, DC seems to be more than just an optional intervention for malignant MCA infarction.

Although this surgical procedure has been validated, few studies have evaluated the effects of DC on cerebral hemodynamics.6–14 Specifically, the hemodynamic effects of DC in patients with MCA infarction remain unclear. Additional knowledge regarding cerebral hemodynamics in different clinical situations will allow us to understand the pathophysiology of the disease and improve the decision-making process for patients with malignant MCA infarctions. Our hypothesis was that DC would improve cerebral hemodynamics and, in patients with favorable outcomes, would have greater hemodynamic improvement. Therefore, we used pre- and postoperative perfusion CT (PCT) to investigate the hemodynamic changes that may occur in patients with malignant MCA infarction after DC and their relationship with outcomes. The absolute values of mean transit time (MTT), cerebral blood flow (CBF), and cerebral blood volume (CBV) were used to assess the hemodynamic changes after DC, whereas the ratios of the post- and preoperative parameters of MTT, CBF, and CBV were used to assess whether the level of hemodynamic improvement was related to outcomes.

Subjects and Methods

This was a single-center, prospective cohort study. The patients were consecutively enrolled at the emergency room of a tertiary hospital. The recruitment period was from January 2008 to September 2012, and the patients had a 6-month follow-up after the surgical procedure.
PCT Protocol

PCT tests were performed using a 64-channel multidetector CT scanner (Philips Medical Systems World Headquarters, Best, the Netherlands). Dynamic conventional scans were obtained in a plane parallel to the orbitomeatal orientation that included the basal ganglia, the thalamus, and parts of the anterior, middle, and posterior cerebral arterial. The acquisition lasted 50 seconds and began 5 seconds after an intravenous infusion of 50 mL iodinated contrast (concentration 300 mg/mL) via an injection pump, which was administered at a rate of 4 mL/s. The imaging parameters were 80 kV and 200 mA. The images were acquired in a helicoidal cine mode at a rate of 1 image per second and were analyzed manually using the General Electric CT Perfusion Software. The arterial and venous input regions of interest (ROIs) were selected. The contralateral anterior cerebral artery and the superior sagittal sinus of the ischemic region were also identified. Color maps were then obtained using a corrective technique to eliminate vascular pixels. For quantitative analysis, four 380-pixel ROIs ipsilateral to the ischemic region (ROIs 1, 2, 3, and 4) and 4 mirror ROIs in the contralateral hemisphere (ROIs 5, 6, 7, and 8) were selected. Of the 4 ROIs that were initially selected for the affected hemisphere, 1 was located in the central area of the infarct (ROI 1), and 3 (ROIs 2, 3, and 4) were positioned proximal to the ischemic area (low attenuation on unenhanced CT), defined as peri-infarct zone (PIZ). The postoperative PCT, for example, because of patient movement during the examination. The patients included in this study underwent nonenhanced head CT and PCT before and 24 hours after the surgical procedure and a standardized DC with a minimum anteroposterior diameter of 120 mm.\(^3\)

Outcome Measures

The changes in cerebral hemodynamics were chosen as our primary dependent variable according to the PCT parameters. The secondary outcomes were consciousness recovery <7 days, mortality at 1 and 6 months, and modified Rankin Scale score at 6 months, which was dichotomized as either a favorable (0–3) or unfavorable (4–6) outcome.

Statistical Analysis

The trial was originally designed to identify an increase of 50% in CBF after DC. A sample of 22 patients was calculated to provide \(\alpha=5\%\) and a power of 80%. Considering the possibility of a 20% loss during follow-up, we recruited 5 additional patients. To compare the pre- and postoperative mean MTT, CBF, and CBV values, we applied the paired \(t\) test for normal distributions and the Wilcoxon test for nonnormal distributions. To identify the level of hemodynamic change, the ratio between post- and preoperative absolute values of global MTT, CBF, and CBV was calculated (\(\Delta\text{MTT, CBF, CBV}\)). We applied the nonpaired \(t\) test for normal distributions and the Mann–Whitney test for nonnormal distributions. We used the Kolmogorov–Smirnov test to assess the normality of the sample. The \(t\) test for independent samples or the \(\chi^2\) test was used to detect associations between independent variables and outcomes. Predefined subgroup analyses were performed according to age (dichotomized at 55 years), time to surgery (dichotomized at 48 hours), and preoperative midline shift (MLS; dichotomized at 10 mm). The significance level was chosen as 0.05. The analyses were performed using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

The study profile is shown in Figure 1. Of the 41 recruited patients, 27 (8 men and 19 women) were included in the final analysis. The average age of our cohort was 52.3±12.4 (mean±SD) years. The time between symptom onset and surgery was 44.6±25.2 hours, and 14 (51.9%) patients underwent surgery <48 hours of ictus. The median preoperative Glasgow Coma Scale score was 10 (interquartile range, 9–11), the median National Institute of Health Stroke Scale was 28.9;[509x218]

Global PCT Analysis Before and After DC

For a global PCT analysis, the preoperative ROIs (1–8) were compared with the corresponding postoperative ROIs (1–8; Figure 2). DC led to a significant reduction in MTT from 8.74 seconds (95% confidence interval [CI], 8.2–9.3) to 8.24 seconds (95% CI, 7.6–8.8; \(P=0.01\)) and a nonsignificant trend toward an increase in CBF from 22.37 mL/min per 100 g (95% CI, 20.3–24.4) to 25.26 mL/min per 100 g (95% CI, 21.7–28.9; \(P=0.06\)). There was no significant difference between the CBV before and after treatment (2.14 versus 2.26 mL/min,

Figure 1. Flow diagram of the study.
respectively, \( P = 0.53 \); Figure 3). The focal PCT analyses are shown in the Table.

**PCT Parameters and Clinical Outcomes**

None of the perfusion variables were associated with the recovery of consciousness <7 days or a fatal outcome <30 days. However, both global pre- and postoperative MTT were associated with a fatal outcome at 6 months (\( P = 0.04 \) and 0.03, respectively). The mean postoperative MTT was 7.6 seconds (95% CI, 6.41–8.79) in patients with a favorable prognosis and 8.52 seconds (95% CI, 7.75–9.28) in patients with a poor prognosis. However, this result was not statistically significant (\( P = 0.17 \)). When evaluating the degree of change in the PCT parameters after DC, the rCBF was significantly associated with prognosis as dichotomized by the modified Rankin Scale (increase of 28%; 95% CI, +9% to +46% in patients with favorable prognosis versus increase of 9%; 95% CI, −11% to +29% in patients with unfavorable prognosis; \( P = 0.049 \)). In patients who had a favorable prognosis, the postoperative CBV increased by 16.6% (95% CI, −4% to +37%) versus 3% (95% CI, −12% to +18%) in patients with unfavorable prognosis. However, this association was not statistically significant (\( P = 0.08 \)).

**Subgroup Analysis**

At 6 months after the operation, age >55 years was associated with an unfavorable prognosis (\( P = 0.03 \)) and mortality (\( P = 0.03 \)). Patients who underwent surgery <48 hours and those with preoperative CT scans showing MLS <10 mm experienced a significant reduction in MTT after DC (\( P = 0.008 \) and 0.04, respectively). Interestingly, patients <55 years of age had a tendency toward greater hemodynamic benefits in terms of both MTT (\( P = 0.06 \)) and CBF (\( P = 0.14 \); Figure 4).

**Discussion**

The present study demonstrated that DC for malignant MCA infarction is associated with improvements in global cerebral hemodynamics. The reduction of MTT was more pronounced in the contralateral hemisphere, whereas the increase in CBF was more significant in the ipsilateral hemisphere. However, the best response to DC was in the PIZ, which revealed a significant improvement in both MTT and CBF. Interestingly, both pre- and postoperative MTT were associated with mortality at 6 months after the operation. After DC, the overall reduction in MTT was not evident in patients who underwent surgery >48 hour after ictus, in those with preoperative MLS >10 mm or in those >55 years of age.

In MCA ischemic stroke, previous PCT studies identified patients with greater potential for progression to malignant MCA infarction who therefore required surgical treatment.15,16 The after-surgery hemodynamic evaluation in such diseases is restricted to a single case report, in which the authors demonstrated improved cerebral hemodynamics using a qualitative PCT method involving color perfusion maps.10 In our study, we evaluated a series of 27 patients and performed a systematic quantitative analysis technique in which a better assessment of both hemispheres and the PIZ was possible. Furthermore, performing PCT <24 hours after treatment allowed us to make more confident inferences that the changes in PCT were secondary to the surgical procedure and were not just because of the healing process. Studies have shown that beyond promoting the reduction of intracranial pressure,17 DC also improves brain hemodynamics.9,10,12,13 Bor-Seng-Shu et al12 demonstrated that in patients with head injuries there is an increase of blood flow velocity in both hemispheres after DC, as assessed using transcranial Doppler. Similarly, using PET in patients with ischemic stroke, Yamakami et al9 showed an increase in CBF after DC. Moreover, Jaeger et al18 showed that DC increases oxygenation levels ipsilateral to the ischemia. These authors found that brain oxygenation was significantly correlated with MTT. Furthermore, the variations in intracranial pressure promoted by DC led to changes in cerebral perfusion pressure.19 Specifically, the PCT parameters most sensitive to subtle changes in cerebral perfusion pressure were MTT and CBF.20 In an experimental study, DC led to an increase in cortical perfusion caused by leptomeningeal arteries.21 In general, these findings may explain our results of increased CBF and reduced MTT after surgery, especially in the PIZ. We emphasize that increases in CBF or CBV do not necessarily represent hemodynamic improvement per se because these increases can be caused by vasospasm or hyperemia, which also have deleterious effects on the brain.13,21 However, when associated with a reduction in MTT, we infer that an increase in CBF or CBV is beneficial. Another interesting and original finding was that the amount of hemodynamic improvement, as expressed by the change in CBF, seems to be related to outcome. Specifically, patients who had greater improvement of CBF had better prognosis. Although several
studies have attempted to explain the changes that occur in CBV, this parameter is difficult to analyze.\textsuperscript{22,23} CBV reflects cerebral autoregulation because it is more deeply associated with vasoconstriction and vasodilatation.\textsuperscript{23} Because patients with extensive infarction can have impaired autoregulation, the absence of a change in CBV may be because of either the persistence of this impairment or the decreased sensitivity to acute changes after surgery.\textsuperscript{24} A late PCT study could confirm this hypothesis.

It was somewhat surprising that the cerebral perfusion patterns after DC did not improve uniformly in all patients in our cohort. Those patients operated >48 hours after stroke, those with MLS >10 mm, and those >55 years of age showed no significant improvement in any perfusion parameters. Several studies have shown better outcomes in patients who received immediate operations\textsuperscript{5} and worse functional outcome in patients with preoperative MLS >10 mm and in the elderly.\textsuperscript{25} Therefore, a reduction in the ability to restore cerebral hemodynamics is a factor that indicates poorer prognosis in these patients. Patients with malignant MCA infarction who operated 48 hours after a stroke have a greater risk of developing increased intracranial pressure because of the large volume of the infarcted area. Studies have shown that cerebral autoregulation is impaired ipsilateral to the MCA infarct.\textsuperscript{26} In a Doppler study, Reinhard et al\textsuperscript{26} also found that autoregulation tends to be impaired 48 hours after a stroke. This impairment subsequently expands to the contralateral hemisphere, which can worsen the prognosis. Furthermore, Dohmen et al\textsuperscript{27} found that an impairment in autoregulation is significantly correlated with preoperative MLS. Thus, there may be an unsatisfactory hemodynamic response in such patients. Moreover, experimental and human studies have suggested that cerebral autoregulation is reduced with age because the lower limit of CBF increases.\textsuperscript{28,29} In addition, Agarwal et al\textsuperscript{30} demonstrated that despite more expressive collateral vessels, the ischemic tissue of elderly patients progressed more rapidly in the infarct core. Thus, although collateral circulation improves with age, it is insufficient to maintain viable tissues in a patient with ischemic stroke.

The association between pre- and postoperative MTT and mortality suggests that this parameter is a potential surrogate marker. However, to verify this assumption, a study with additional patients is necessary.

This study has some limitations. The number of patients included in this study was relatively small, although this study has the largest sample of patients submitted to DC who were evaluated with PCT. In addition, the hemodynamic study was only performed with PCT. The use of transcranial Doppler or CT angiography could allow further evaluation of cerebral collateral circulation and the occurrence of recanalization. Because surgical treatment was performed as needed, at any time of the day, the use of Doppler was not feasible because it could only be performed during the day. Additionally, because CT angiography requires additional exposure to radiation and intravenous iodinated contrast, we preferred not to use it because the patients would have been exposed to 2 PCT studies over a relatively short duration. Furthermore, the ROIs

### Table. Comparison Between the Mean of Absolute Values of Perfusion CT Variables Before and After DC

<table>
<thead>
<tr>
<th>Variables</th>
<th>Before DC</th>
<th>After DC</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ipsilateral hemisphere</strong> (corresponding ROIs 1, 2, 3, and 4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTT, s (95% CI)</td>
<td>9.61 (8.9–10.3)</td>
<td>9.21 (8.4–9.9)</td>
<td>0.07</td>
</tr>
<tr>
<td>CBF, mL/min per 100 g (95% CI)</td>
<td>17.6 (15.6–19.6)</td>
<td>20.7 (17.5–24.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>CBV, mL/min (95% CI)</td>
<td>1.85 (1.64–2.05)</td>
<td>1.99 (1.67–2.37)</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Contralateral hemisphere</strong> (corresponding ROIs 5, 6, 7, and 8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTT, s (95% CI)</td>
<td>7.87 (7.3–8.4)</td>
<td>7.28 (6.6–7.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>CBF, mL/min per 100 g (95% CI)</td>
<td>27.13 (24.3–29.9)</td>
<td>29.83 (25.3–34.3)</td>
<td>0.12</td>
</tr>
<tr>
<td>CBV, mL/min (95% CI)</td>
<td>2.44 (2.21–2.68)</td>
<td>2.54 (2.23–2.85)</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>Peri-infarct zone</strong> (corresponding ROIs 2, 3, and 4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTT, s (95% CI)</td>
<td>9.3 (8.51–10.1)</td>
<td>8.67 (7.92–9.42)</td>
<td>0.01</td>
</tr>
<tr>
<td>CBF, mL/min per 100 g (95% CI)</td>
<td>21.53 (19.24–23.81)</td>
<td>25.10 (21.46–28.74)</td>
<td>0.03</td>
</tr>
<tr>
<td>CBV, mL/min (95% CI)</td>
<td>2.26 (2.01–2.52)</td>
<td>2.39 (2.01–2.77)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

CBF indicates cerebral blood flow; CBV, cerebral blood volume; CI, confidence interval; DC, decompressive craniectomy; MTT, mean transit time; and ROI, region of interest.
Figure 4. Box-plot showing changes in the global mean transit time (MTT; regions of interest [ROIs], 1–8) after decompressive craniectomy (DC) according to age (≤55 vs >55 y) and time between ictus and surgery (≤48 vs >48 h; P=0.06 and 0.008, respectively).

were chosen based on the degree of hypoattenuation visualized via CT, which increases the possibility of nonviable tissue being included in the PIZ. However, we did not intend to evaluate the effects of DC in the penumbra area in or in the infarcted region; instead, we focused on the overall effects on both hemispheres. Another limitation of our study was that 34% of eligible patients were excluded, primarily because of poor postoperative examination quality and the severity of their disease. The latter prevented the completion of PCT for 24 hours after the surgery. Additionally, observer variation was not assessed, which could decrease the validity of our findings. However, some studies have shown that the use of a specific and standardized postprocessing protocol causes a minimal amount of variability in CT perfusion results among the observers.31–34 These issues were associated with the fact that this study was conducted in a single center, which may compromise the generalizability of the data.

Conclusions

This study provides further pathophysiological consistency of the clinical findings of patients with malignant MCA infarction submitted to DC. In addition, PCT analysis may assist neurosurgeons and neurologists in decision making to define the best candidates for DC or in discussing prognostic aspects with relatives.

Disclosures

None.

References


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