ORIGINAL RESEARCH

CT perfusion-guided patient selection for endovascular treatment of acute ischemic stroke is safe and effective

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ABSTRACT
Background Traditional treatment in acute ischemic stroke is based on time criteria when administering intravenous and intra-arterial therapies. However, recent evidence suggests that image-based criteria may be useful for selecting patients for intra-arterial interventions. The use of CT perfusion (CTP)-based criteria, regardless of time from symptom onset, in patient selection for intra-arterial treatment of ischemic stroke was assessed.

Methods Patients with ischemic stroke who presented to the emergency department at the Medical University of South Carolina with a National Institute of Health Stroke Scale score of ≥8, regardless of time from symptom onset, were assessed retrospectively. CTP maps were qualitatively assessed for the presence of penumbra and infarction. Selected patients underwent mechanical aspiration of their occlusion using the Penumbra system. Functional outcome was then recorded using the modified Rankin scale (mRS) at 90 days or the closest follow-up to 90 days.

Results 53 patients were included in the study. The median time from symptom onset to groin vascular access was 6.3 h. Eight patients (15%) had bleeding complications including subarachnoid hemorrhage, parenchymal hemorrhage and intraventricular hemorrhage. After CTP-based selection, the patients were divided into two groups for analysis: ≤6 h and >6 h from symptom onset to endovascular procedure. No difference was found in functional outcome between the two groups (38.5% and 40.7% achieved 90-day mRS ≤2, respectively (p=1.0) and 57.7% and 51.9% achieved 90-day mRS ≤3, respectively (p=0.785)). There was no difference in the rate of intracranial hemorrhage between the two groups (11.5 vs 18.5, p=0.704).

Conclusion This study demonstrated similar rates of good functional outcome and intracranial hemorrhage in patients with ischemic stroke when endovascular treatment was performed based on CTP selection rather than time-guided selection. These findings suggest that endovascular perfusion in ischemic stroke may be effective and safe, and may allow patient selection not solely based on time from symptom onset.

BACKGROUND
Current recommendations for the recanalization of patients with acute ischemic stroke are based on time-defined parameters. Intravenous tissue plasminogen activator (tPA) administration is indicated within 3 h of symptom onset, with newer evidence suggesting that tPA may be beneficial up to 4.5 h.1–4 In addition, intra-arterial thrombolysis within 6 h has been shown to be effective in vessel recanalization and in improving patient outcomes while thrombectomy devices may be effective up to 8 h from symptom onset.5–10 Several recent reports have suggested that, with imaging-based selection, patients may be effectively treated beyond these strict time boundaries with good outcomes.11–14

To date, non-contrast head computed tomography (NCCT) is the principal imaging modality for suspected acute ischemic stroke. More recently the acquisition of qualitative physiologic data with CT perfusion imaging (CTP) has improved the sensitivity and specificity of identifying acute infarctions and penumbral regions.15–19 Current trials such as the mechanical retrieval and recanalization of stroke clots using embolectomy (MR RESCUE) and the efficacy and safety study of desmoteplase to treat acute ischemic stroke (DIAS-3) are evaluating the utility of perfusion imaging to select patients with acute stroke for treatment without traditional time limitations. We report the experience at our center using CTP-based imaging to select patients with acute ischemic stroke for endovascular recanalization, irrespective of time constraints.

MATERIALS AND METHODS
An Institutional Review Board-approved retrospective review of a prospectively managed clinical database was performed for all cases of acute ischemic stroke intervention performed from 1 January 2008 to 31 December 2009. Chart review was further performed to assess the clinical course and outcome.

A retrospective chart review was performed through an electronic medical record. Patient characteristics documented included age, race, gender, National Institute of Health Stroke Scale Score (NIHSSS) at presentation, time to presentation from last normal and modified Rankin Score (mRS) at 90 days or closest follow-up period to 90 days. Modified Rankin Score data were obtained from the neurology clinic record. If the medical record did not contain outcome information, an independent neurologist contacted the patient or family to
Ischemic stroke
determine the functional status of the patient in order to
determine the mRS. Radiological and angiographic imaging were
reviewed to document location of vascular occlusion, recanal-
ization time, TIMI flow post-procedure, procedural complica-
tions and the presence of intracerebral hemorrhage post- or peri-
procedurally.

Patient selection
All stroke patients presenting with NIHSS ≥8, irrespective of
time of symptom onset, were considered candidates for endo-
vascular therapy. All patients underwent NCCT, CT angiog-
raphy (CTA) and CTP on admission to the emergency
department. The NCCT scan was used to determine the pres-
ence and extent of gross infarction and to exclude underlying
pathology such as mass orintracranial hemorrhage (ICH). CTA
was used to identify the location of vascular occlusion. CTP
was analyzed to identify the presence and extent of penumbra relat-
tive to the core area of infarction. The primary endpoints of the
study were the percentage achieving good functional outcome as
measured by 90-day mRS ≤2 and mRS ≤3. The primary safety
endpoints were symptomatic ICH (sICH) within 36 h and
mortality at 90 days.

CTP imaging techniques
All CT imaging was performed according to a standardized
institutional protocol. All CTP scans were performed using a
Siemens 64- or 16-slice scanner with a 50 ml Omnipaque 350
(GE Healthcare, Milwaukee, WI, USA) contrast bolus. Perfusion
datasets were post processed on a GE Advantage Windows
Workstation (General Electric; Milwaukee, Wisconsin, USA),
Siemens Leonardo Workstation (Siemens Medical, Germany), or
both. CTA was subsequently performed with an 80 ml bolus
injection of contrast followed by a saline chase. Two-dimen-
sional 1 cm thick slab reformations were created in the axial,
sagittal and coronal projections. These data were used to localize
the location of the major vessel occlusion.

Data processing
CTP after processing on the GE workstation was performed by
a radiology resident or by an experienced CT technologist
yielding mean transit time (MTT), cerebral blood volume (CBV)
and cerebral blood flow (CBF) maps. CTP after processing on the
Siemens workstation was performed by an experienced CT
technologist. MTT, CBV and CBF maps were reconstructed. The
arterial input and venous outflow curves were analyzed to
ensure complete data sets. All CTP interpretations for treatment
endpoints were made by the attending neurointerventionalist based
on qualitative interpretation of the perfusion maps. MTT maps
were analyzed to define the area of brain at risk as delineated by
at least two color band differences on the six-spectrum rainbow
scale from the surrounding unaffected brain. CBV was evaluated
to delineate the core region of infarction as the area with
depressed CBV at least two color band differences on the six-
spectrum rainbow scale from the surrounding unaffected brain.
CBF was used to confirm these findings and further define the
area at risk. Patients in whom one-third or more of the MCA
territory was infarcted or with ≤50% penumbra were not
considered candidates for endovascular treatment unless an
elquent area was at risk.

Endovascular treatment
Written informed consent for endovascular therapy was
obtained in all cases. All cases were performed under general
anesthesia. Patients received heparin in a 1500-unit bolus
followed by a 500-unit bolus every hour thereafter. The primary
method of treatment in most cases was mechanical aspiration
with the Penumbra aspiration system. The approach that
evolved over the first 10 cases was to use the largest caliber
aspiration catheter that the occluded vessel would accommo-
date. Intra-arterial thrombolysis with tPA was used adjunctively
at low doses ranging from 10 to 20 mg (administered in 5–5 mg
aliquots) during the procedure if aspiration was not immediately
effective. In patients who presented within the 0–3 or 3–4.5 h
time windows, intravenous tPA was administered to eligible
patients before going to the angiography suite. Intra-arterial
abciximab was administered if acute intraprocedural thrombus
formation was felt to be present. If a permanent stent was used
either to recanalize the thrombosed vessel or to treat a proximal
stenosis, the patient was given a weight-based loading dose of
abciximab and 325 mg aspirin and 600 mg clopidogrel were
administered immediately after the procedure. All patients were
managed postoperatively in the neurosurgical intensive care unit
for at least the first 24 h after the endovascular procedure to
ensure strict blood pressure monitoring and control.

Data analysis
Baseline demographic, radiographic and outcomes data were
analyzed using descriptive statistics including means, standard
deviations, frequencies, percentages and medians. Comparisons
between time to treatment groups were made using two-sided t
tests for continuous measures, χ2 tests for categorical measures
and Mann–Whitney U tests for non-parametric measures
(medians). No adjustments were made for multiple comparisons
and p values <0.05 were considered significant.

RESULTS
Fifty-three patients underwent endovascular treatment, with 18
receiving intravenous tPA prior to intra-arterial therapy. The
overall mean age was 65 years (median 66 years) and 49% of
patients were men. The mean NIHSS at presentation to our
institution was 17.2 (median 17) and the locations of vascular
occlusion were 22.6% internal carotid artery, 60.4% middle
cerebral artery (MCA) and 17.0% posterior circulation (basilar
artery or posterior inferior cerebellar artery) (table 1).

The mean time from the last point the patient was seen
normal to groin vascular access was 10.4 h (median 6.5 h, range
1.75–72 h). The mean time to obtain working access with a
guide catheter from puncture was 20 min and to obtain TIMI
II revascularization was 41.4 min. Revascularization rates were
60% TIMI III, 36% TIMI II and 4% TIMI I. The devices used to
achieve revascularization in 48 patients were: Penumbra 054
(n=5), Penumbra 041 (n=16), Penumbra 032 (n=14), Penumbra

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>53</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>65.0</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>66.0</td>
</tr>
<tr>
<td>Gender, M/F (%)</td>
<td>49/51</td>
</tr>
<tr>
<td>Mean admission NIHSS</td>
<td>17.2</td>
</tr>
<tr>
<td>Median admission NIHSS</td>
<td>17.0</td>
</tr>
<tr>
<td>Location of vascular occlusion (%)</td>
<td></td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td>22.6</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>60.4</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>17.0</td>
</tr>
<tr>
<td>Received intravenous tPA prior to intervention (%)</td>
<td>34</td>
</tr>
</tbody>
</table>

NIHSS, National Institute of Health Stroke Scale Score; tPA, tissue
plasminogen activator.
Overall, eight patients (15%) had bleeding complications including subarachnoid hemorrhage, parenchymal hemorrhage and intraventricular hemorrhage. Four of these patients had sICH giving an incidence of 8%. There were three procedure-related complications which included two (3.7%) intracranial vessel perforations and a non-flow limiting carotid dissection related to guide catheter excision. Follow-up NCCT scans at 24 h demonstrated SAH in an additional two patients, which were probably due to unrecognized procedural dissections or perforations. Hyperdensity in the basal ganglia was noted on five 24 h post-procedural CT scans. These hyperdensities all resolved the following day and were felt to represent contrast staining of the basal ganglia rather than hemorrhage.

Patients were initially selected for endovascular procedures based on CTP criteria and then analyzed based on time from symptom onset to procedure. The patients were divided into two groups: ≤6 h and >6 h from symptom onset to neuro-interventional procedure. There were no significant differences in age, race or gender between the groups (table 2). The mean NIHSS scores were 19.1 and 15.3 (p=0.025), respectively, for the two groups. For the two time periods, 38.5% and 40.7% achieved a 90-day mRS ≤2 (p=0.362), and 57.7% and 51.9% (p=0.785) achieved a 90-day mRS ≤3 (table 2). In addition, the percentage mortality as measured by an mRS of 6 at 90-day follow-up was 15.4 versus 29.6 (p=0.327) and the rate of ICH was 11.5 versus 18.5 (p=0.704) for the two groups (table 2).

When recanalizations were categorized into complete, partial or no recanalization, the ≤6 h group achieved recanalization rates of 61.5%, 33.3%, and 7.4%, respectively (p=0.327), and 59.3%, 33.3% and 7.4%, respectively (p=0.362), respectively, for the two groups. For the two time periods, 38.5% and 40.7% achieved a 90-day mRS ≤2 (p=0.362), and 57.7% and 51.9% (p=0.785) achieved a 90-day mRS ≤3 (table 2). In addition, the percentage mortality as measured by an mRS of 6 at 90-day follow-up was 15.4 versus 29.6 (p=0.327) and the rate of ICH was 11.5 versus 18.5 (p=0.704) for the two groups (table 2).

When recanalizations were categorized into complete, partial or no recanalization, the ≤6 h group achieved recanalization rates of 61.5%, 33.3%, and 7.4%, respectively. In the >6 h time group the percentages of complete, partial and no recanalization were 59.3%, 33.3%, and 7.4%, respectively (p=0.362). Location of vessel occlusion was a consideration in the analysis for both groups. In the ≤6 h time group the rates of internal carotid artery, middle cerebral artery and posterior circulation (basilar artery and posterior inferior cerebellar artery) occlusions were 23.1%, 61.5%, and 15.4%, respectively compared with 22.2%, 59.3% and 18.5%, respectively, in the >6 h time group (p=0.955, table 2).

### Table 2

Comparison of treatment and outcomes between the two study groups: those treated ≤6 h versus those treated >6 h from symptom onset

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Time to treatment</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤6 h (N = 26)</td>
<td>&gt;6 h (N = 27)</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>8 (30.8)</td>
<td>12 (44.4)</td>
</tr>
<tr>
<td>Caucasian American</td>
<td>17 (65.4)</td>
<td>15 (55.6)</td>
</tr>
<tr>
<td>Hispanic American</td>
<td>1 (3.8)</td>
<td>0</td>
</tr>
<tr>
<td>Gender, M/F (%)</td>
<td>12/14 (46.2/53.8)</td>
<td>14/13 (51.9/48.1)</td>
</tr>
<tr>
<td>Median time to treatment (h)</td>
<td>4.0</td>
<td>5.5</td>
</tr>
<tr>
<td>90-day mRS ≤2</td>
<td>10 (38.5)</td>
<td>11 (40.7)</td>
</tr>
<tr>
<td>90-day mRS ≤3</td>
<td>15 (57.7)</td>
<td>14 (51.9)</td>
</tr>
<tr>
<td>Mortality</td>
<td>4 (15.4)</td>
<td>9 (29.6)</td>
</tr>
<tr>
<td>Intravenous tPA</td>
<td>13 (50.0)</td>
<td>5 (18.5)</td>
</tr>
<tr>
<td>Recanalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>16 (61.5)</td>
<td>16 (59.3)</td>
</tr>
<tr>
<td>Partial</td>
<td>10 (38.5)</td>
<td>9 (33.3)</td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>Mean NIHSS</td>
<td>19.1</td>
<td>15.3</td>
</tr>
<tr>
<td>Location of occlusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td>6 (23.1)</td>
<td>6 (22.2)</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>16 (61.5)</td>
<td>16 (59.3)</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>4 (15.4)</td>
<td>5 (18.5)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>3 (11.5)</td>
<td>5 (18.5)</td>
</tr>
</tbody>
</table>

mRS, modified Rankin Score; NIHSS, National Institute of Health Stroke Scale Score; tPA, tissue plasminogen activator.
Revascularized patients achieved mRS ≤2 compared with 10% of non-revascularized patients (p<0.001). This study also showed a significant increase in 90-day mortality in patients who were not revascularized compared with those who were able to be revascularized (52% vs 25%, p<0.001). Similarly, the Penumbra POST Trial found that 45% of patients who were revascularized achieved a mRS ≤2 compared with 13% of patients who were not successfully recanalized. We demonstrated similar rates of good functional outcome regardless of whether patients were treated endovascularly before or after 6 h from symptom onset. Our study found that 38.5% and 40.7% of patients treated before and after 6 h, respectively, achieved a 90-day mRS ≤2. Also, when recanalization is considered, all patients treated ≤6 h from symptom onset achieved either partial or total recanalization. For patients treated >6 h from symptom onset, 93% achieved either partial (TIMI II) or total recanalization (TIMI III).

Revascularization is crucial for improved outcomes, so appropriate patient selection for revascularization therapies is paramount. Non-contrast CT scanning of the head has been the primary imaging modality in evaluating patients with acute stroke as it can screen for ICH and demonstrate early ischemic changes that might prevent patients from receiving intravenous tPA. The pattern of ischemic changes may be able to predict patients who will have a good functional outcome using the Alberta Stroke Program Early CT Score. However, the widespread acceptance of NCCT and the Alberta Stroke Program Early CT Score alone for stroke triage has been limited. This probably relates to the subtlety of acute ischemia in many instances on non-contrast CT scanning that can be difficult to detect.

The use of CTP has been advocated over the last decade as a physiologic tool and, when used in conjunction with non-contrast CT scanning, can identify the area of infarction through CBV maps and further define the penumbral region by integrating MTT data. The use of this physiologic approach to select patients within a specified time window is currently being studied in several randomized trials. This approach is also being applied to everyday practice to help select patients who present outside conventional time windows. We have also used this technique over the last several years to triage all stroke patients for potential intra-arterial therapy. We found that using CTP for selecting stroke patients allowed us to treat many patients who would not otherwise be considered candidates for therapy. This is best understood by comparing the two groups based on median time to presentation of ≤6 h or >6 h. When imaging criteria are used, 38.5% of patients treated ≤6 h from symptom onset achieved mRS ≤2 and 40.7% of patients treated >6 h from symptom onset achieved mRS ≤2 (p=1.0). If we broaden our definition of good outcome to mRS ≤3, which still portends a functional lifestyle, in acute ischemic stroke the same trend continues with 57.7% and 51.9% of patients treated ≤6 h and >6 h, respectively, achieving 90-day mRS ≤3 (p=0.785). Our overall ICH rate was 15% with 8% sICH. This compares favorably with that seen in the previous device trials as well as reports from investigators treating similar patient populations. When stratifying our patient population to ≤6 h versus >6 h, we found similar rates of ICH (11.5% vs 18.5%, p=0.704) and mortality (15.4% vs 29.6%, p=0.327). While significance was not achieved, the overall small size of our study population and the even smaller number of patients experiencing ICH or death limit our ability to conclude whether or not patients treated >6 h from symptom onset achieved statistically similar rates of ICH and death as those treated ≤6 h. We recommend further study with a larger patient cohort to determine if rates of ICH and death are in fact similar between the two groups.

Our overall mortality rate was 23% which is similar to that in previous trials (HAMLET, DECIMAL, DESTINY). Additionally, the median admission NIHSS score was 17, demonstrating that our patient selection was not heavily weighted towards those with lower severity stroke. The causes for the favorable result probably relate to patient selection, where we followed prior European Cooperative Acute Stroke Study (ECASS) recommendations and excluded patients with large infarctions (more than one-third MCA territory) and selected those with relatively large penumbral volume as evidenced by CTP. Performing thrombectomy primarily with a device and then the relatively judicious use of intra-arterial tPA also probably contributed to the low rates of ICH. Close management in a dedicated neurocritical care unit may further contribute to improved outcomes.

Other limitations of this study include the retrospective nature of the data collection in a prospectively maintained patient database. Some patients had follow-up done by telephone interview and beyond 90 days, which could allow a bias to better outcome. The fact that we did not track the outcomes of the patients that we excluded based on penumbral imaging meant we were unable to compare the outcome with this group. Also, the significant differences in the mean admission NIHSS score between the ≤6 h and >6 h patient groups (19.1 vs 15.3, p=0.025) demonstrates that, while those in the later time group had statistically different NIHSS scores, this difference is less significant from a clinical standpoint since the mean scores in both groups were highly indicative of increased stroke severity. Furthermore, a previous study that stratified admission NIHSS score of ≤7 versus >7 determined that those with an admission NIHSS >7 (as in our patient cohort) were less likely to improve neurologically and functionally.

In addition, the use of perfusion imaging for patient triage could potentially bias the early group as some patients may have been excluded who otherwise would be included in comparative studies based on time parameters. The lack of a quantifiable methodology of CTP data for patient selection and the qualitative application of this approach by multiple physicians may weaken its applicability.

The practical application of physiologic imaging to select patients for acute stroke interventions irrespective of time was safe and effective in our single-center experience, with patient outcomes similar to those seen in other trials of acute stroke. The strongest evidence is the similar rates of good clinical outcomes (mRS ≤2 and ≤3) in patients treated ≤6 h compared with those treated >6 h from symptom onset. The application of this approach may have a significant impact on the number of patients eligible for beneficial interventional therapy, especially those initially presenting to rural or community hospitals who are often ineligible for thrombolytic treatment.

Competing interests None.

Ethics approval This study was conducted with the approval of the Medical University of South Carolina Institutional Review Board (exempt status).

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES


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