A Comparison of Computed Tomography Perfusion-Guided and Time-Guided Endovascular Treatments for Patients With Acute Ischemic Stroke

Ameer E. Hassan, DO; Haralabos Zacharatos, DO; Gustavo J. Rodriguez, MD; Gabriela Vazquez, PhD; Jefferson T. Miley, MD; Ramachandra P. Tummala, MD; M. Fareed K. Suri, MD; Robert A. Taylor, MD; Adnan I. Qureshi, MD

Background and Purpose—The role of CT perfusion (CT-P) imaging for the selection of patients with acute ischemic stroke who may benefit from endovascular treatment is not defined. The objective of this study was to determine whether CT-P-guided endovascular treatment improves clinical outcomes compared with standard endovascular treatment based on the time interval between symptom onset and presentation and noncontrast cranial CT imaging.

Methods—A retrospective study was performed comparing the clinical characteristics, complications, and clinical outcomes of patients with acute ischemic stroke who were treated using endovascular modalities based on either CT-P imaging (CT-P-guided) or time interval between symptom onset and presentation and absence of intracerebral hemorrhage or extensive ischemic changes on noncontrast cranial CT scan (time-guided).

Results—The rates of partial and complete recanalization were similar between the CT-P- and time-guided treatment groups (n=61 [88%] versus n=103 [81%]; P=0.52) regardless of whether they received intravenous recombinant tissue plasminogen activator before endovascular treatment. Comparing the CT-P-guided with the time-guided patients, favorable discharge outcome (modified Rankin Scale 0 to 2) was observed in 23 (32%) versus 41 (33%) of the patients, respectively (P=0.9). In-hospital mortality was observed in 15 (21%) of CT-P- and 29 (23%) of time-guided patients (P=0.74).

Conclusion—CT-P-guided endovascular treatment did not increase the rate of short-term favorable outcomes among patients with acute ischemic stroke. Prospective studies are required to validate the CT-P criteria and protocols currently in use before incorporating CT-P as a routine modality for patient selection for endovascular treatment. (Stroke. 2010; 41:1673-1678.)

Key Words: acute ischemic stroke ■ computed tomographic perfusion ■ endovascular treatment ■ thrombectomy ■ thrombolysis

Noncontrast cranial CT scan findings in patients with acute ischemic stroke have been classically used to select patients for intravenous and endovascular thrombolysis therapy in the European Cooperative Acute Stroke Study (ECASS)1 I, II, and III,1 Interventional Management of Stroke (IMS) I,4 II5 and III,6 Prolyse in Acute Cerebral Thromboembolism (PROACT) II,7 and Mechanical Embolus Removal in Cerebral Ischemia (MERCI)8 trials. Ezzeddine et al9 found that CT perfusion (CT-P) imaging was more sensitive (100%) and specific (92%) than noncontrast CT (93% sensitive and 67% specific) for the detection of large ischemic infarcts (affecting greater than one third of the affected lobe). Similarly, Wintermark et al10 found that dynamic CT-P images were more accurate than nonenhanced cranial CT in the detection of ischemic stroke in patients presenting with symptoms <12 hours in duration. Subsequently, new emphasis has been placed on using CT-P imaging to select patients with acute ischemic stroke who can benefit from endovascular treatment. Selection is based on identification of hypoperfused, hypoxic tissue that is structurally intact and at risk of infarction but potentially salvageable with early reperfusion (penumbra). The presence of ischemic penumbra on CT-P can be identified based on increased mean transit time (MTT), decreased regional cerebral blood flow (rCBF), and normal or increased regional cerebral blood volume (rCBV)11 and potentially used to select patients with acute ischemic stroke for intravenous12 or endovascular treatment.13

The 2009 American Heart Association Scientific Statement14 recommends that a vascular imaging study should not delay the start of intravenous thrombolysis in patients with ischemic stroke presenting within 3 hours of symptom onset. The American Heart Association statement suggests that CT-P may be used to select patients for intravenous...
thrombolysis treatment beyond a strict 3-hour time window. However, CT-P has not been validated for use in the diagnosis of penumbra and identification of patients appropriate for endovascular treatment. The goal of our study was to determine if there is an incremental clinical benefit to CT-P-guided selection compared with standard time-guided selection of patients with acute ischemic stroke undergoing endovascular treatment.

Materials and Methods
A retrospective study of consecutive endovascularly treated acute ischemic stroke patients was performed between January 1, 2007, to July 1, 2009, at the University of Minnesota and Hennepin County Medical Centers and from May 2005 to July 2007 at the University of Medicine and Dentistry of New Jersey. The 3 institutions maintained a prospective endovascular procedure database. The protocol for collecting data was reviewed and approved by the Institutional Review Board at each institution as part of a standardized database.

Patient Selection
At the University of Medicine and Dentistry of New Jersey, all patients were selected for endovascular treatment based on time interval between symptom onset and hospital presentation and noncontrast cranial CT scan findings. Every patient had a noncontrast CT scan to identify intracranial hemorrhage (ICH), cerebral edema, sulcal effacement, dense vessel sign, focal parenchymal hypointensity, or an obvious infarction of greater than one third of the middle cerebral artery vascular territory.

At the University of Minnesota and Hennepin County Medical Centers, the majority of endovascularly treated patients were selected after undergoing CT angiogram and CT-P scans. The CT-P protocol started with a noncontrast cranial CT scan and was discontinued if ICH was identified. Most perfusion scans were performed on the Phillips 64-slice CT scanner. Maps obtained by the Phillips 64 (Phillips Medical Systems, Cleveland, OH) were generated using both Gaussian fit and single value deconvolution methods using Vitrea software (Vital Images), yielding the following perfusion parameters: time to peak, MTT, rCBF, and rCBV. Patients were selected for endovascular treatment based on qualitative and quantitative analysis demonstrating preserved rCBV, decreased rCBF, and increased MTT in ≥20% of the affected region and involving the cortex. Automated quantitative values for rCBF, rCBV, and MTT in predefined regions of interest were infrequently used as supplementary data to enhance the identification of mismatch based on the previously published parameters by Wintermark et al15,16: MTT >145% of the contralateral side values and rCBV >2 mL/100 g.15,16

In the case of a middle cerebral artery vascular territory infarction, the patient was excluded from endovascular treatment if the infarct burden was greater than or equal to one third of the vascular territory on qualitative analysis of the rCBV map acquired from the previously published parameters by Wintermark et al15,16; MTT >145% of the contralateral side values and rCBV >2 mL/100 g.15,16

Data Collected
We recorded the presence of cardiovascular risk factors (active smoking history, hypertension, atrial fibrillation, coronary artery disease, hyperlipidemia, diabetes mellitus, prior transient ischemic attack or ischemic stroke), time interval between symptom onset and endovascular intervention, and use of intravenous recombinant tissue plasminogen activator. We also recorded admission, 24-hour post-treatment, and discharge National Institutes of Health Stroke Scale (NIHSS) scores, and discharge modified Rankin Scale scores. The principal safety end points were ICH and in-hospital mortality. Symptomatic ICH was defined as noncontrast CT scan-documented ICH either in the area of the qualifying stroke and related to neurological deterioration (≥2-point worsening on a NIHSS score compared with previous clinical assessment) or in a different vascular territory and associated with new neurological deficits within 24 hours of treatment. Early neurological improvement was documented as an improvement in NIHSS score ≥4 or a NIHSS score of 0 at 24 hours posttreatment. Favorable functional outcome was defined by modified Rankin Scale score of 0 to 2 at discharge.

Angiographic Recanalization
Arterial occlusion on pre- and posttreatment cerebral angiogram was classified by the Qureshi Grading Scale, a previously validated grading scheme based on the occlusion location and collateral supply to the affected region.20,21 The Qureshi Grading Scale has 6 grades with Grade 0 denoting no occlusion and Grade 5 representing complete occlusion of either the internal carotid artery or the basilar artery. Recanalization was defined by a reduction in ≥1 grade from baseline in the Qureshi Grading Scale consistent with previous studies.22–24

Statistical Analysis
All data were descriptively presented using mean±SD for continuous data and frequencies for categorical data. The frequency of baseline demographic and clinical characteristics, admission NIHSS score, time interval between symptom onset and endovascular treatment, and the interval between hospital presentation and endovascular treatment were compared between acute ischemic stroke patients treated using CT-P- and time-guided selection criteria. Statistical association was assessed with 1 test or median 2-sample test according to normality for continuous data and χ2 test for categorical data. The rates of partial and complete angiographic recanalization, symptomatic and asymptomatic ICHs, early neurological improvement, favorable discharge outcome, and in-hospital mortality were compared. Multivariable analysis was not performed because all potential confounding factors were similar between the 2 groups.

Results
A total of 69 patients (mean age±SD 68±15 years; n=36 [52%] men) underwent CT-P-guided and 127 patients (mean age±SD 65±15 years; n=65 [51%] men) underwent time-guided endovascular treatment. The clinical characteristics and mean NIHSS score on admission were similar between the 2 groups (Table 1). There was no difference with regard to the median time interval between symptom onset and endovascular treatment between the CT-P- and time-guided treatment groups: 308 minutes (range, 140 to 1120, n=65 of 69) versus 301 minutes (range, 116 to 1109, n=107 of 127; P=0.87).

The rates of various endovascular treatments used are presented in Table 1. The rate of postprocedural partial and complete recanalization was similar between the patients treated using CT-P- and time-guided selection (n=61 [88%] versus n=103 [81%]; P=0.52). Before endovascular treatment, intravenous recombinant tissue plasminogen activator was administered to 32 (44%) of the CT-P-guided patients compared with 47 (37%) of the time-guided patients (P=0.3). Intravenous recombinant tissue plasminogen activator administration was not associated with a higher rate of recanalization (P=0.29) or favorable outcome at discharge (P=0.53).

Favorable outcome was observed in 23 (32%) CT-P-guided and 41 (33%) time-guided treatment patients (P=0.9; Table 2). Early neurological improvement was observed in 46 (64%) of the CT-P-guided and 69 (64%) of 108 time-guided endovascularly treated patients (P=0.94). In-hospital mortal-
ity rates among CT-P-guided and time-guided treatment patients were similar: 15 (21%) versus 29 (23%; \( P = 0.74 \); Table 2). Among patients with acute ischemic stroke undergoing CT-P- or time-guided treatment, there was no difference in the rates of symptomatic (9/73 [12%] versus 8/75 [10%]; \( P = 0.59 \)) or asymptomatic ICHs (11 [15%] versus 13 [10%]; \( P = 0.29 \); Table 2). There were no differences observed in the rates of partial or complete recanalization, favorable outcome at discharge, neurological improvement, or symptomatic or asymptomatic ICHs in patient strata based on time interval between symptom onset and treatment (≤6 and >6 hours) between the 2 groups (Table 2).

**Discussion**

We compared the clinical outcomes of patients with acute ischemic stroke selected for endovascular intervention based on either CT-P- or time-guided paradigms. There was no difference in the proportion of factors that could obscure any differential rates of outcomes between the 2 groups, including admission NIHSS score, median time interval between symptom onset and endovascular treatment, or rates of partial or complete recanalization. When compared with the time-guided endovascularly treated patients, CT-P-guided patients were not found to have an increased clinical benefit with respect to functional outcome, early neurological improvement, ICH, and in-hospital mortality. Furthermore, no difference was observed in patients presenting to the hospital within or after 6 hours of symptom onset.

Although the primary purpose of the noncontrast cranial CT scan is to exclude any ICH, findings of early ischemic injury such as sulcal effacement, obscuration of junction between gray and white matter, and focal parenchymal low attenuation have been used to identify patients at risk for poor outcomes after thrombolysis.25 The extent of early ischemic changes on noncontrast CT scan has been quantified using the Alberta Stroke Program Early CT26 scoring system (ASPECTS). The ASPECTS score is a 10-point scale that rates the presence or absence of ischemia in 10 regions of the brain. In a post hoc analysis of the PROACT-II7 study, patients with ischemic stroke with a baseline ASPECTS ≥7 were 3 times more likely to have an independent functional outcome with thrombolytic treatment compared with control subjects.37 Experienced endovascular physicians may be able to use the findings on noncontrast CT scan supplanted by information regarding time interval between symptom onset and presentation and other unmeasured variables such as the mismatch between clinical deficits and CT scan findings to appropriately identify patients with ischemic stroke who may benefit from endovascular treatment. Such selection criteria may limit the value of CT-P-guided selection of patients for thrombolytic treatment, particularly endovascular treatment.
The concept is similar to the selection of patients for thrombolytic therapy based on mismatch between deficits observed in diffusion- and perfusion-weighted MRI. Previous studies of patients with acute ischemic stroke demonstrated CT-P measurements of MTT, rCBF, and rCBV correlate well with concurrent assessment using perfusion-weighted MRI. However, the information regarding viability of regional tissue provided by diffusion-weighted MRI is not directly available by CT-P. Wintermark et al studied 42 patients with ischemic stroke who successively underwent CT angiogram and CT-P and MRI examinations within 3 to 9 hours of symptom onset and found that there was an excellent interobserver agreement for CT-P with respect to infarct size, cortical involvement, arterial occlusion site, and magnitude of mismatch denoting penumbra to infarct ratio.

CT-P evaluation of patients with ischemic stroke, beyond the initial 6 hours of symptom onset, has been used to select patients appropriate for endovascular treatment. Natarajan et al reported the results of endovascular therapy in 30 patients with ischemic stroke who successively underwent CT angiogram and CT-P and MRI examinations within 3 to 9 hours of symptom onset and found that there was an excellent interobserver agreement for CT-P with respect to infarct size, cortical involvement, arterial occlusion site, and magnitude of mismatch denoting penumbra to infarct ratio.

The mismatch between rCBV and rCBF deficits on CT-P may not represent salvageable tissue. Animal models studying the pathophysiology of ischemic and infarcted brain tissue have demonstrated that irreversible stereotypical biochemical, molecular, and electrophysiological changes occur as rCBF is reduced for a prolonged period of time. In contrast to infarcted tissue, the penumbra retains its biochemical, molecular, and electrophysiological function despite decreased cerebral perfusion. The presence of collateral circulation may contribute to the maintenance of cerebral perfusion and rCBV within the affected brain region; unfortunately, collateral circulation is variable and may not always be present.

### Table 2: Rates of Various Outcomes Among Patients Treated Using CT-P-Guided and Time-Guided Endovascular Treatments

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Patients Undergoing CT-P-Guided Treatment (n=69)</th>
<th>Patients Undergoing Time-Guided Treatment (n=127)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable outcome at discharge, no.</td>
<td>23 (32%)</td>
<td>41 (33%)</td>
<td>0.90</td>
</tr>
<tr>
<td>Early neurological improvement, no.</td>
<td>46 (64%)</td>
<td>69 (64%), 108</td>
<td>0.94</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>15 (21%)</td>
<td>29 (23%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>6 (8%)</td>
<td>8 (6%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Asymptomatic ICH</td>
<td>11 (15%)</td>
<td>13 (10%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Partial or complete recanalization</td>
<td>61 (88%)</td>
<td>103 (81%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Endovascular treatment ≤6 hours of symptom onset</td>
<td>(n=36)</td>
<td>(n=75)</td>
<td></td>
</tr>
<tr>
<td>Favorable outcome at discharge</td>
<td>15 (42%)</td>
<td>27 (36%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Early neurological improvement, no.</td>
<td>25 (69%)</td>
<td>50 (74%), 67</td>
<td>0.65</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>6 (17%)</td>
<td>15 (20%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>3 (8%)</td>
<td>7 (9%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Asymptomatic ICH</td>
<td>4 (11%)</td>
<td>8 (11%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Partial or complete recanalization</td>
<td>30 (83%)</td>
<td>68 (91%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Endovascular treatment &gt;6 hours of symptom onset</td>
<td>(n=33)</td>
<td>(n=52)</td>
<td></td>
</tr>
<tr>
<td>Favorable outcome at discharge</td>
<td>7 (21%)</td>
<td>14 (27%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Early neurological improvement, no.</td>
<td>19 (58%)</td>
<td>19 (46%), 41</td>
<td>0.36</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>9 (27%)</td>
<td>14 (27%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>3 (9%)</td>
<td>1 (2%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Asymptomatic ICH</td>
<td>6 (18%)</td>
<td>5 (10%)</td>
<td>0.32</td>
</tr>
<tr>
<td>Partial or complete recanalization</td>
<td>28 (85%)</td>
<td>35 (67%)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

There are limitations to acquisition and interpretation of CT-P imaging in the current study. Multislice CT scanners provide 2 to 4 cm of coverage per acquisition, which do not always allow the evaluation of the exact perfusion deficit volumes if they exceed the volume studied. The variation in reconstruction of CT-P images and qualitative interpretation of salvageable tissue may lead to selection of a relatively heterogeneous population, leading to the inclusion of patients with limited salvageable tissue, which may obscure the benefit of endovascular treatment. False-negatives and uninterpretable imaging can be obtained when using CT-P imaging largely due to a patient’s low cardiac output, inappropriate slow rate of bolus administration, contrast extravasation in the subcutaneous tissue, patient movement, and operator inexperience. No definitive comments can be made regarding efficacy due to the absence of a comparison group.

The mismatch between rCBV and rCBF deficits on CT-P may not represent salvageable tissue. Animal models studying the pathophysiology of ischemic and infarcted brain tissue have demonstrated that irreversible stereotypical biochemical, molecular, and electrophysiological changes occur as rCBF is reduced for a prolonged period of time. In contrast to infarcted tissue, the penumbra retains its biochemical, molecular, and electrophysiological function despite decreased cerebral perfusion. The presence of collateral circulation may contribute to the maintenance of cerebral perfusion and rCBV within the affected brain region; unfortunately, collateral circulation is variable and may not always be present.
This was a retrospective study with a sample size that was not adequate to establish a noninferiority of CT-P over time-guided selection of patients appropriate for endovascular therapy. Due to the fact that this was not a randomized study, there may be unmeasured differences between the 2 treatment groups. We did not document the number of patients who were excluded from endovascular treatment based on either the CT-P or noncontrast cranial CT findings in either of the treatment paradigms. Although the magnitude of this selection bias is not known, preferential selection of the best possible candidates would have favored better outcomes among the CT-P-guided group. It should be noted that intravenous recombinant tissue plasminogen activator was not withheld in study sites based on CT-P findings consistent with current guidelines and may have obscured the potential differences in outcomes between the 2 groups. Because the CT-P-guided treatments occurred more recently than the time-guided treatment, evolution in both endovascular technology and standardization of postprocedural medical care would also have favored the CT-P-guided treatment group. However, the lack of standardized and validated criteria based on CT-P confounded by interpretation by multiple physicians may have undermined the value of CT-P-guided treatment. There may also have been some patients with pre-existing deficits and modified Rankin Scale scores of 3 to 5 who could not have demonstrated a favorable discharge modified Rankin Scale score of 0 to 2 despite treatment. However, the proportion of patients with a history of prior strokes was similar between the 2 patient groups.

Conclusion
CT-P-guided endovascular treatment (compared with conventional time-guided endovascular treatment) was not associated with improved short-term outcomes among patients with acute ischemic stroke. There are currently no randomized controlled trials that demonstrate incremental benefit using CT-P-guided selection of patients for endovascular treatment. Prospective studies are required to validate the CT-P criteria and protocols currently in use before incorporating CT-P as a routine patient selection modality for endovascular treatment.

Sources of Funding
A.I.Q. has received funding from National Institutes of Health RO-1-NS44976-1A2 (medication provided by ESP Pharma), American Heart Association Established Investigator Award 0840053N, and Minnesota Medical Foundation, Minneapolis, Minn.

Disclosures
None.

References


A Comparison of Computed Tomography Perfusion-Guided and Time-Guided Endovascular Treatments for Patients With Acute Ischemic Stroke

Stroke. 2010;41:1673-1678; originally published online July 8, 2010;
doi: 10.1161/STROKEAHA.110.586685

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/41/8/1673

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/