CT Angiography With Whole Brain Perfused Blood Volume Imaging

Added Clinical Value in the Assessment of Acute Stroke

Mustapha A. Ezzeddine, MD; Michael H. Lev, MD; Colin T. McDonald, MD; Guy Rordorf, MD; Jamary Oliveira-Filho, MD; Fatma Gul Aksoy, MD; Jeffrey Farkas, MD; Alan Z. Segal, MD; Lee H. Schwamm, MD; R. Gilberto Gonzalez, MD, PhD; Walter J. Koroshetz, MD

Background and Purpose—In CT angiographic and perfusion imaging (CTA/CTP), rapid CT scanning is performed during the brief steady state administration of a contrast bolus, creating both vascular phase images of the major intracranial vessels and perfused blood volume–weighted parenchymal phase images of the entire brain. We assessed the added clinical value of the data provided by CTA/CTP over that of clinical examination and noncontrast CT (NCCT) alone.

Methods—NCCT and CTA/CTP imaging was performed in 40 patients presenting with an acute stroke. Short clinical vignettes were retrospectively prepared. After concurrent review of the vignettes and NCCT, a stroke neurologist rated infarct location, vascular territory, vessel(s) occluded, and Trial of Org 10172 in Acute Stroke Treatment (TOAST) and Oxfordshire Community Stroke Project classifications. The ratings were repeated after serial review of each of the CTA/CTP components: (1) axial CTA source images; (2) CTP whole brain blood volume–weighted source images; and (3) maximum-intensity projection 3-dimensional reformatted images. The sequential ratings for each case were compared with the final discharge assessment.

Results—Compared with the initial review after NCCT, CTA/CTP improved the overall accuracy of infarct localization (P<0.001), vascular territory determination (P=0.003), vessel occlusion identification (P<0.001), TOAST classification (P=0.039), and Oxfordshire Community Stroke Project classification (P<0.001) by 40%, 28%, 38%, 18%, and 32%, respectively.

Conclusions—Admission CTA/CTP imaging significantly improves accuracy, over that of initial clinical assessment and NCCT imaging alone, in the determination of infarct localization, site of vascular occlusion, and Oxfordshire classification in acute stroke patients. (Stroke. 2002;33:959-966.)

Key Words: angiography ■ diagnostic imaging ■ stroke assessment ■ stroke classification ■ tomography, x-ray computed
CTA/CTP has multiple potential advantages in the evaluation of early stroke. Combined with NCCT, CTA/CTP can be rapidly obtained with minimal delay in treatment. It is widely available in emergency departments. Almost all patients tolerate the study well. The CTA portion of the examination is highly accurate in identifying major occlusions of the intracranial vasculature. The CTP portion of the examination, obtained simultaneously with the angiographic portion with the use of the same bolus of contrast, provides axial whole brain perfused blood volume–weighted images. These 2 components make CTA/CTP a valuable tool in the detection of ischemic stroke, permitting the localization of the precise site of vascular occlusion, as well as the identification of hypodense territories likely to be irreversibly infarcted.

In this study we have attempted to assess the added clinical value of CTA/CTP imaging, over that of the clinical examination and NCCT alone, in the initial evaluation of acute stroke. An accurate assessment of the specific stroke subtype and the involved vascular lesion and territory at risk may help to guide physician-patient discussions and research regarding the prognosis and treatment of acute stroke patients.

Subjects and Methods

All patients who presented to the emergency department with an acute stroke syndrome between January 1997 and December 1998 were identified from a database maintained by the stroke neurology service. Forty consecutive patients who received a CTA/CTP exam were included in the study. Several patients were excluded because of missing angiographic data.4 All patients were instructed to choose which brain regions were affected (stroke location). In addition, they specified the area of involvement as less than one third, one third to two thirds, or more than two thirds of a lobe. Involvement of the corona radiata, internal capsule, deep gray matter, cerebellum, and brain stem was recorded as either “minor” or “major” (arbitrarily designated by reviewer according to the expected size of the lesion). Size was graded by visual inspection. The affected vascular territory was specified as anterior cerebral artery, middle cerebral artery (MCA) stem, MCA superior division, MCA inferior division, MCA perforators, posterior cerebral artery, verte-
brosal artery, or border zone. Trial of Org 10172 in Acute Stroke Treatment (TOAST) and modified Oxfordshire Community Stroke Project classifications (adjusted to imaging findings) were determined according to published criteria. The site of vascular occlusion was chosen from internal carotid artery (ICA)/M1 (ICA/MCA stem), M2 (MCA M2 division), M3 (MCA M3 branches), perforators (MCA perforators), vertebrobasilar, or none.

Specifics of image review by the rating neurologists are as follows: Both the NCCT and CTP images were evaluated by changing the window width and center level visual review settings to accentuate potentially subtle foci of low attenuation. The 3-mm collimated axial source CTA images were reformatted into 1-mm overlapping axial images (12-cm field of view). These 1-mm reformatted images were transferred to a freestanding Advantage Windows Workstation (GE Medical Systems) for further postprocessing. One of the authors prospectively reconstructed the 1-mm axial source images into standardized axial “collapsed” MIP 3-dimensional views of the circle of Willis.

The statistical significance of the difference between the final, “correct” impressions and the impressions based on the NCCT and combined CTA images (axial images, CTP, and 3-dimensional MIP reconstructions) was tested with the McNemar test. The incremental contribution of each component of CTA toward the improvement in diagnostic accuracy was also tested with the McNemar test. We computed 95% CIs on the basis of the binomial distribution. To account for multiple comparisons in each of our diagnostic categories (4 comparisons per category), we used an adjusted \( P \) value of 0.0125 (=0.05/4) as a cutoff for establishing statistical significance.

The institution’s internal review board for human subject studies approved this study.

Results

Forty patients were included in this study (17 women and 23 men). Mean age was 71 years (SD 12); median National Institutes of Health Stroke Scale score was 14; median time from onset to NCCT/CTA/CTP was 2 hours 52 minutes (mean, 4 hours 38 minutes; SD 4 hours 37 minutes). Seventeen patients underwent imaging within 3 hours of symptom onset, 16 patients between 3 and 6 hours, and 7 patients between 6 and 24 hours. Fourteen patients received thrombolytic therapy. The follow-up study was an NCCT in 33 patients and an MRI in 7. Mean time to follow-up was 3.3 days (SD 1.9 days).

According to the modified Oxfordshire Community Stroke Project classification at discharge, 9 patients had a total anterior circulation syndrome (TACS), 14 a partial anterior circulation syndrome (PACS), 5 a lacunar syndrome (LACS), and 4 a posterior circulation syndrome (POCS). Four patients who did not have a stroke were diagnosed with transient ischemic attack (n=3) or complex partial seizure (n=1).

For all 5 clinical categories (location of the infarct, vascular territory affected, vessel involved, TOAST and Oxfordshire stroke classifications), the assessments based on the CTA/CTP images matched the final clinical impressions better than did the assessments based on the NCCT images (Figure 2; 95% CIs, based on binomial distribution, are shown in Table 1). The use of CTA/CTP, compared with clinical examination and NCCT alone, significantly improved diagnostic accuracy in the following clinical categories: location of infarct, vascular territory, vessel occluded, and Oxfordshire stroke classification (Tables 1 and 2). The TOAST results approached, but did not reach, statistical significance, with a critical \( P \) value threshold of 0.0125 used for multiple comparisons.

To determine which components of the CTA/CTP examination individually provided a statistically significant improvement over that of the initial impression, we compared (1) the axial NCCT images to the axial CTA circle of Willis source images, (2) the axial CTA source images to the optimally windowed CTP images, and (3) the CTP images to the 3-dimensional CTA MIP reformatted images. Incremental
improvement in accuracy was statistically significant after incorporation of CTP images for the following diagnostic categories: (1) location of infarct, (2) vascular territory, and (3) Oxfordshire classification (Table 2). Again, the TOAST results for incorporation of the CTP source images for the vessel occlusion category approached, but did not reach, statistical significance, with a critical P value threshold of 0.0125 used for multiple comparisons.

We additionally examined whether the improvement in diagnostic accuracy with CTA/CTP, over NCCT, was more substantial for any specific diagnoses. Twelve patients had a major infarct in the M1 territory. All were identified as such by CTA/CTP; 11 were identified by NCCT. Of the 7 infarcts in the lenticulostriate vessels (M1 perforators), CTA/CTP identified 5, and NCCT identified 2 (Figure 3).

CTA/CTP improved prediction of the vascular lesions. CTA/CTP identified all 15 cases of top of the ICA/M1 occlusion, whereas NCCT identified only 12. CTA/CTP also identified all 8 cases of M2 occlusions, whereas NCCT identified only 3. CTA/CTP and NCCT performed poorly in identifying the 5 patients who did not have a stroke (correctly identifying only 3. CTA/CTP and NCCT performed poorly in identifying the 5 patients who did not have a stroke (correctly identifying only 3). CTA/CTP identified all 15 cases of top of the ICA/M1 occlusion, whereas NCCT identified only 12. CTA/CTP also identified all 8 cases of M2 occlusions, whereas NCCT identified only 3. CTA/CTP and NCCT performed poorly in identifying the 5 patients who did not have a stroke (correctly identifying only 3). CTA/CTP and NCCT performed poorly in identifying the 5 patients who did not have a stroke (correctly identifying only 3).

As a measure of its validity as a triage tool, we tested the ability of CTA/CTP to accurately predict which patients were likely to have small versus large infarcts. Final stroke was considered small if it involved less than one third of a lobe or only a minor infarct in the basal ganglia, corona radiata, or internal capsule, with no more than 1 lobe or brain area (basal ganglia, internal capsule, centrum semiovale, thalamus, cerebellum, brain stem) affected. Cases with greater brain involvement were considered large strokes. By this definition, CTA/CTP was 100% sensitive (95% CI, 87.7% to 100%) and 92% specific (95% CI, 61.5% to 99.8%) for the detection of large infarcts. In comparison, NCCT was 93% sensitive (95% CI, 76.5% to 99.1%) and 67% specific (95% CI, 34.9% to 97.5%), although the difference from CTA/CTP did not reach statistical significance.

### Discussion

The ability to rapidly and accurately delineate the pathophysiology of an acute ischemic insult in the emergency setting is of great clinical value. Overall long-term outcome could be better anticipated, facilitating more rational tailoring of therapeutic interventions to the individual patient. The potential for more accurate prognostication regarding the risks and benefits of thrombolytic therapy would also be of value. With the increasing research interest in customizing treatment of specific stroke subtypes, the improved ability to correctly classify an infarct on initial presentation could additionally enhance patient selection for clinical trials.

The accuracy of CTA in the assessment of cerebrovascular disease has been demonstrated by direct comparison to both digital subtraction arteriography and MR angiography. The use of CTA in acute stroke has been reported as a means of identification of patients with autolized thrombi, occlusion

### Table 1. Percentage of Cases Correctly Interpreted for Cumulative Impressions After the Sequential Incorporation of Each Imaging Component

<table>
<thead>
<tr>
<th></th>
<th>Stroke Localization</th>
<th>Vascular Territory</th>
<th>Vessel Occluded</th>
<th>TOAST Classification</th>
<th>Oxfordshire Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTA axial source images</td>
<td>43 (27–59)</td>
<td>55 (38–71)</td>
<td>60 (43–75)</td>
<td>83 (67–93)</td>
<td>63 (46–77)</td>
</tr>
<tr>
<td>Perfused blood volume CTA source images</td>
<td>79 (64–91)</td>
<td>79 (64–91)</td>
<td>72 (56–85)</td>
<td>85 (67–93)</td>
<td>87 (70–94)</td>
</tr>
<tr>
<td>MIP reconstruction from CTA data set</td>
<td>80 (64–91)</td>
<td>83 (64–91)</td>
<td>78 (62–89)</td>
<td>85 (67–93)</td>
<td>88 (73–96)</td>
</tr>
</tbody>
</table>

Values are percentage correct (95% CI calculated on the basis of the binomial distribution).

### Table 2. Level of Statistical Significance in Improvement of Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Stroke Localization</th>
<th>Vascular Territory</th>
<th>Vessel Occluded</th>
<th>TOAST Classification</th>
<th>Oxfordshire Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCCT vs CTA/CTP</td>
<td>&lt;0.001</td>
<td>0.003</td>
<td>&lt;0.001</td>
<td>0.039</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NCCT vs CTA</td>
<td>1.000</td>
<td>1.000</td>
<td>0.039</td>
<td>0.031</td>
<td>0.250</td>
</tr>
<tr>
<td>CTA vs CTP</td>
<td>&lt;0.001</td>
<td>0.006</td>
<td>0.125</td>
<td>1.000</td>
<td>0.006</td>
</tr>
<tr>
<td>CTP vs MIP</td>
<td>1.000</td>
<td>1.000</td>
<td>0.500</td>
<td>1.000</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Values are P values of the McNemar test. To account for multiple comparisons, only P values <0.0125 were considered statistically significant. First row compares the cumulative impression after review of all components of the CTA/CTP study with that obtained from NCCT and clinical information alone. Rows 2, 3, and 4 evaluate the incremental value of sequentially incorporating the components of the contrast study.
of the ICA bifurcation, and poor leptomeningeal collaterals.\textsuperscript{14} However, few studies have documented its value in the clinical assessment of acute stroke patients. In this report we have shown that CTA/CTP improved the accuracy of stroke diagnosis over that of clinical examination and NCCT alone, as measured by the following diagnostic categories: stroke localization, site of vascular occlusion, and commonly used classification schemes (Oxfordshire and TOAST).

**Postcontrast Axial Source CTA Images**

The first component of the CTA that we reviewed, postcontrast axial source images through the circle of Willis, made only a minimal contribution to the accuracy of stroke localization. CTA alone provided little information about brain tissue viability. It showed a trend toward facilitating the identification of the site of vascular occlusion, although this relationship did not reach statistical significance. Together with the clinical data, the accuracy of CTA in this respect was 60% compared with 40% for NCCT. Accuracy was limited by the inability of the axial images to reliably identify smaller branches, ie, lenticulostriate or basilar perforators. In identifying large-vessel (defined as ICA, M1, M2, vertebrobasilar) occlusions, the accuracy of the axial postcontrast images was 85%.

**CTP Source Images**

CTP images (postcontrast whole brain perfused blood volume axial source images) are obtained by continuing to scan above the circle of Willis so as to include the entire brain. Areas with a critical drop in cerebral blood volume appear hypodense on CTP, effectively delineating regions of ischemia.\textsuperscript{21} Thus, CTP dramatically improved stroke localization, from approximately 40% to 80% accuracy. Together with knowledge of the vascular anatomy, this improved localization translated into improved stroke classification. Conversely, CTP also improved assessment of occluded vessel identification; for example, in one case a hypodense CTP lesion throughout the superior division of the MCA territory led to the diagnosis of M2 branch occlusion as the likely underlying vascular lesion, despite the fact that a somewhat distal M2 thrombus was difficult to detect on the CTA images. Because we did not perform precise volumetric analysis with coregistration of the various initial and follow-up imaging studies, our estimation of the accuracy of localization is based on visual inspection. The goal of this study was not to precisely correlate the final infarct volume with that of the initial perfusion lesion (which has been done in other studies) but to assess the value of CTA/CTP in daily clinical practice.\textsuperscript{21}

**Three-Dimensional MIP Reconstructed Images**

Although they contain the data with which the 3-dimensional MIP reconstructions are assembled, considerable experience is required to identify M2 or distal posterior cerebral artery occlusions on the source postcontrast CTA circle of Willis.

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**Figure 3.** Number of cases with correct vascular territory involvement diagnosis. Final diagnosis was added to show the total number of cases. m1 indicates MCA stem; maj, major; min, minor; m2, second division of MCA; m1 perf, MCA perforators; m3, distal branches of MCA; and post, posterior circulation. Other abbreviations are as defined in Figure 2.

**Figure 4.** Number of cases with correct vascular lesion identified. Final diagnosis was added to show the total number of cases. ICA/m1 indicates ICA/MCA stem; m2, second division of MCA; m3, distal branches of MCA; perforators, perforator branches of the m1 or of the basilar artery; and vertbas, vertebrobasilar. Other abbreviations are as defined in Figure 2.
images. On CTA, vessels typically opacify distal to the sites of occlusion, so that detection of a short segment of absent contrast enhancement in a vessel curving in or out of the axial imaging plane is required to detect a vascular occlusion. Three-dimensional MIP reconstructions of the circle of Willis, which can be obtained in under 1 minute on most 3-dimensional workstations (but not on all scanner consoles), make identification of such distal, short-segment vascular occlusions much more straightforward, with an accuracy approaching or exceeding 95%, depending on the patient population studied.20

The MIP reformatted images were the last set of images reviewed in our study protocol. Because they were presented after the whole brain postcontrast axial perfusion images, it is difficult to compare the added value of these images directly with that of the CTA source images. Three-dimensional MIP CTA reconstructions did, however, improve the identification of vascular occlusion beyond that of the axial CTA images and axial CTP (appropriately windowed) images combined.

In previously reported studies, as well as in our experience, 3-dimensional MIP CTA reconstructions have compared favorably with conventional angiography. In 1 study of 145 patients with symptoms of acute stroke, arterial stenoses or occlusions were found to be present on 43% of CT angiograms. For 27 cases in which both CTA and MR angiography were obtained, findings were in agreement for 98% of vessels; agreement was 99% for the 28 cases in which both CTA and digital subtraction angiography were acquired.22

Four patients in our study who presented with acute stroke-like symptoms were proven, on follow-up imaging, to have not had stroke. One of these was ultimately diagnosed with complex partial epilepsy; it was concluded that he had been in a postictal state during initial evaluation. The final discharge diagnosis for the remaining 3 patients was transient ischemic attack. CTP falsely identified 2 of these 3 cases as acute lacunar infarction. These false-positive studies likely resulted from overinterpretation of small fluctuations in CT image density or interpretation of a chronic hypodensity as acute. A “negative” CTA/CTP study was not considered adequate to exclude a small stroke in the setting of an appropriate clinical history. It may, however, suggest a nonstroke diagnosis in a patient with a persistent, major hemispheric syndrome.

In a preliminary attempt to estimate the value of CTA/CTP in the prediction of imaging outcome, we elected to test the

![Figure 6](http://stroke.ahajournals.org/)

**Figure 6.** Eighty-year-old man who presented with sudden-onset left hemiparesis and neglect 2 days after valvuloplasty for aortic stenosis. A, Head NCCT, without definitive signs of acute infarct. B, CTA axial source image shows a filling defect in the distal right MCA stem (arrow). C, CTA axial source image, with window width and center level review settings optimized for assessment of perfused blood volume lesions, reveals a large low-attenuation defect in the right MCA territory (arrows). D, MIP image, reconstructed from the axial CTA source images, again demonstrates occlusion of the distal MCA stem (arrow). E, Follow-up NCCT, obtained 4 days later, shows a large infarct corresponding to the lesion seen on the initial CTA axial source images.
The sequence with which the CTA components were presented for review by the individual raters was chosen to replicate the typical clinical scenario. In clinical practice, the NCCT images are always the first available for review, followed by the circle of Willis source images and the whole brain postcontrast CTP images (optimally windowed), and finally by the MIP reconstructed images. We chose to examine the sequential improvement in diagnostic accuracy after review of each of these CTA components in an attempt to demonstrate the added benefit of each component, as well as of the entire CTA/CTP study as a whole. In the emergency setting, the clinician can review the NCCT images, the axial source images of the circle of Willis, and the whole brain axial CTP source images at the CT console immediately after the completion of scanning. Varying the window width and center level settings at the CT console facilitates delineation of subtle regions of low density, as well as the highlighting of the contrast-filled vessels.2 Although creation of the MIP reconstructions requires postprocessing, this can be accomplished directly at the CT console of our scanner in less than 1 minute.20 While identification of the precise site of vascular occlusion was improved by review of both the axial CTA source images and the MIP reconstructions, stroke localization was mostly influenced by the whole brain postcontrast axial CTP source images, reviewed with the use of optimized window width and center level review settings. In many cases, the involved vessel could be inferred by the distribution of the parenchymal CT perfusion abnormality. Most relevant, however, is the overall improvement in diagnostic accuracy that occurs when all of these CTA/CTP imaging components are combined.

An important potential limitation of our study involves the clinical vignettes with which we attempted to replicate the actual information available to the emergency department physicians. Creation of these vignettes was complicated by the lack of standardized record keeping sometimes present in emergency department reports. Although it is possible that these vignettes provided the raters with more, rather than less, information than was routinely available to the emergency department clinicians, causing the incremental diagnostic value of contrast CT to be underestimated, there is no way to definitively determine in which direction the vignettes were biased. Hence, the vignettes may not accurately reflect the actual clinical situation and are likely to have altered our results in an unpredictable manner.

Another potential limitation of our study involves the determination of the final, gold standard diagnosis, which was based on a composite of all available clinical and imaging data. Although the follow-up CT and MRI exams were the major confirmatory tests used to establish this final diagnosis, awareness of the CTA/CTP results by the reviewers undoubtedly contaminated the gold standard to some degree and may have biased the final impression in favor of CTA/CTP.

Both of these limitations could be overcome by the performance of a randomized, prospective study, in which the reviewers are aware of the admission clinical examination and NCCT findings but blinded to the initial CTA/CTP results and in which the final diagnosis is established independently of the CTA/CTP results. Although such a trial could be logistically difficult to conduct for a variety of reasons, not the least of which would be the appropriate blinding of study participants, this would be necessary for the unbiased confirmation of our conclusions in a more diverse group of stroke patients.

In this study we compared CTA/CTP with the most widely used initial neuroimaging modality, NCCT. MRI, most notably diffusion- and perfusion-weighted imaging, provides more sensitive and specific information regarding potentially infarcted tissue than does NCCT. An MR angiography component can be added to the MRI examination to provide information regarding the vascular occlusion. The exquisitely detailed information derived from these studies is offset, however, by the time delay typically required to obtain an emergency MRI at most institutions. Relative increased cost and lack of widespread accessibility detract from the utility of MRI as a screening tool in the emergency setting. In addition, some patients are excluded from MRI because of claustrophobia, agitation, or cardiac pacemaker. It has been proposed that MRI can be used as the primary examination for acute stroke patients, forgoing the routine NCCT. However, there are insufficient data regarding the percentage of persons excluded from MR study and the cost of using MR to scan every emergency patient suspected of having a recent cerebrovascular event.

CTA/CTP provides an easily accessible, accurate, early, vascular diagnosis that may be of value for therapeutic decisions such as selection of patients for intra-arterial thrombolysis, triage of patients from community clinics to comprehensive stroke centers, or triage of patients from hospital floor beds to neurological intensive care units. The ability to more precisely classify stroke subtypes and to accurately distinguish large-vessel from small-vessel stroke may be important for both prognostication and appropriate enrollment in clinical trials.

In summary, our data suggest that CTA/CTP, performed in acute stroke patients, could be a valuable addition to available diagnostic tools. It provides useful information about the extent of infarction, vascular anatomy, and pathophysiology. By combining data describing the patency of the major cerebral vessels (axial CTA source images and 3-dimensional MIP reconstructions) with data describing brain tissue perfusion (optimally windowed whole brain perfused blood volume postcontrast CTP source images), a more accurate picture of acute stroke pathophysiology in an individual patient can be obtained. In addition to its potential value in subtyping patients for inclusion in stroke research trials, the added data that CTA/CTP provides may assist in the more rational triage of patients to available stroke treatments.

Acknowledgments
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