Perfusion CT Improves Diagnostic Accuracy for Hyperacute Ischemic Stroke in the 3-Hour Window: Study of 100 Patients with Diffusion MRI Confirmation

Ke Lin a, Kinh G. Do a, Phat Ong a, Maksim Shapiro a, James S. Babb a, Keith A. Siller b, Bidyut K. Pramanik a

Departments of a Radiology and b Neurology, New York University Langone Medical Center, New York, N.Y., USA

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Perfusion CT · Hyperacute ischemic stroke · Acute stroke imaging

Abstract

Purpose: Conventional noncontrast CT (NCCT) is insensitive to hyperacute cerebral infarction in the first 3 h. Our aim was to determine if CT perfusion (CTP) can improve diagnostic accuracy over NCCT for patients presenting with stroke symptoms in the 3-hour window. Methods: Consecutive patients presenting to our emergency department with symptoms of ischemic stroke <3 h old and receiving NCCT and CTP as part of their triage evaluation were retrospectively reviewed. Patients with follow-up diffusion-weighted MRI (DWI) <7 days from ictus were included. Two readers rated the NCCT and CTP for evidence of acute infarct and its vascular territory. CTP selectively covered 24 mm of brain centered at the basal ganglia with low relative cerebral blood volume in a region of low cerebral blood flow or elevated time to peak as the operational definition for infarction. A third reader rated all follow-up DWI for acute infarct and its vascular territory as the reference standard. Sensitivity, specificity, and predictive values were calculated. An exact McNemar test and generalized estimating equations from a binary logistic regression model were used to assess the difference in detection rates between modalities. A two-sided p value <0.05 was considered significant. Results: 100 patients were included. Sixty-five (65%) patients had follow-up DWI confirmation of acute infarct. NCCT revealed 17 (26.2%) acute infarcts without false positives. CTP revealed 42 (64.6%) acute infarcts with one false positive. Of the 23 infarcts missed on CTP, 10 (43.5%) were outside the volume of coverage while the remaining 13 (56.5%) were small cortical or lacunar type infarcts (<15 mm in size). CTP was significantly more sensitive (64.6 vs. 26.2%, p < 0.0001) and accurate (76.0 vs. 52%, p < 0.0001) and had a better negative predictive value (59.6 vs. 42.2%, p = 0.032) than NCCT. Conclusion: In a retrospective cohort of 100 patients with symptoms of hyperacute stroke in the 3-hour window, CTP provided improved sensitivity and accuracy over NCCT.

Introduction

MRI with diffusion-weighted imaging (DWI) is more accurate in detecting hyperacute ischemic cerebral infarcts than conventional noncontrast CT (NCCT) [1–4]. Despite this superior accuracy, it remains unclear if MRI should be the initial examination of choice to triage patients presenting with stroke symptoms. Depending on
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the clinical status of the patient and the resources of an urgent care setting, MRI may not always be suitable or available. This has prompted continued interest in developing CT-based modalities for triage given their general advantages of universal availability, speed, and convenience. In the current 3-hour therapeutic window for use of intravenous tissue plasminogen activator (tPA), NCCT is performed primarily to exclude intracerebral hemorrhage and ischemic stroke mimics. There have been several reports of improved accuracy using dynamic CT perfusion (CTP) for hemispheric infarcts in the first 12 h [5, 6] and 6 h [7, 8] after symptom onset. However, the use of intravenous tPA outside the 3-hour window remains a contraindication to date. Our goal was to determine the diagnostic accuracy of CTP for hyperacute infarction in a retrospective cohort of patients presenting with stroke symptoms in the first 3 h and to compare this accuracy to NCCT, using follow-up DWI as the reference standard.

Methods

Patients

Imaging and clinical data obtained as part of standard clinical stroke care at our institution were retrospectively reviewed. Consent was waived for review of all images and charts according to the guidelines of the Institutional Board of Research Associates. From January 2004 to May 2008, 151 consecutive patients presented to our institution’s emergency department within 3 h of onset of symptoms that were suggestive of an acute ischemic stroke and received a ‘CT stroke series’ consisting of NCCT, CTP, and CT angiogram (CTA) as part of routine clinical care. Subsets of these patients had been included in previously published studies [9–11]. Patients were initially included for this analysis if a follow-up MRI of the brain with DWI was performed <7 days from ictus. This primary selection criterion included 109 patients.

Image Acquisitions

All CT examinations were performed on 16-slice scanners (Siemens Sensation, Siemens AG, Erlangen, Germany). NCCT was obtained with 5-mm contiguous axial sections from vertex to skull base using imaging parameters of 120 kVp, 285 mAs, 1.5-mm slice collimation, and 1.0-second rotation. CTP was obtained using two contiguous 12-mm-thick axial sections centered at the level of the basal ganglia and internal capsules for a total of 24 mm of z-axis coverage. This anatomical region was chosen to maximize the inclusion of the middle cerebral artery (MCA) territory, while also including portions of the brain supplied by the anterior cerebral artery and posterior cerebral artery (PCA). A 60-second cine series was performed beginning 4 s after the intravenous administration of 50 ml of iodinated contrast at 5 ml/s by a power injector into an antecubital vein (Omnipaque, 300 mg iodine/ml; Amersham Health, Princeton, N.J., USA). CTP parameters were 80 kVp, 200 mAs, 0.5-second rotation, and 60 images per section. All follow-up MRI exams were performed on 1.5-tesla systems (Siemens Vision or Symphony, Siemens AG). DWI parameters were TR 3,400 ms, TE 95 ms, b values of 0, 100, 1,000 s/mm², 5-mm images at 5-mm slice intervals, 128 × 128 matrix, and 6 gradient directions.

Data Acquisition

Raw CTP source images were retrieved from our institution’s picture archived and communication system (PACS; Siemens Medical Solutions, Erlangen, Germany) onto an offline workstation (Siemens Leonardo, Siemens AG) equipped with postprocessing software that generates color overlay maps of dynamic enhancement data (Siemens Syngo Neuro Perfusion CT, Siemens AG). This software calculates the perfusion metrics of cerebral blood flow (CBF), cerebral blood volume (CBV), and time to peak (TTP) using tissue and blood time attenuation curves as previously described [5, 12, 13]. Patients were further excluded if the dynamic CTP data was degraded by poor injection (n = 3), severe motion artifacts (n = 4), or cutoff of the venous input curve before returning to baseline (n = 2). The remaining dynamic datasets from 100 unique patients were used to generate CBF, CBV, and TTP parametric color maps in 256 × 256 matrix. The color scales were set at 0–100 ml/100 ml/s for all CBF maps, 0–6 ml/100 ml for all CBV maps, and 0–20 s for all TTP maps.

Data Analysis

Two board-certified radiologists (each with approximately 1-year experience in CTP interpretation) reviewed in consensus each set of CTP color maps and NCCT, in alternating, random, patient order. The criterion for hyperacute infarction on CTP maps (examined on the workstation) was a lesion with low relative CBV in a focal region of elevated TTP or decreased CBF compared to the homologous region in the contralateral hemisphere. The criteria for hyperacute infarction on NCCT (examined on our PACS) were hypointensity or loss of gray-white distinction in the basal ganglia, loss of the insula cortical ribbon or obscuration of the sylvian fissure, any cortical sulcal effacement, any focal hypointensity compared to the homologous structure in the contralateral hemisphere not compatible with chronic infarction, and hyperintensity of an artery greater than that of any other vessel [14]. The readers were instructed to examine the NCCT in standard brain windows (center = 40 Hounsfield units, width = 80 Hounsfield units) followed by a second evaluation in which window widths and center level settings were freely adjusted to optimize gray-white distinction [15]. The readers were aware that all patients arrived to the emergency room <3 h from symptom onset and that an infarct, if present, may involve more than one vascular territory. They were blinded to all other clinical information, formally dictated reports, and follow-up imaging data. For both CTP and NCCT, the readers indicated on a spreadsheet (Excel 2003, version 11.6560, Microsoft, Seattle, Wash., USA) whether an infarct was present, and if so, its laterality and vascular distribution. One board-certified radiologist examined each patient’s follow-up whole-brain DWI and corresponding apparent diffusion coefficient maps on PACS for evidence of acute infarction. Similarly, if an infarct was present, its laterality and vascular territory were recorded on a spreadsheet.

Statistical Analysis

A detection of hyperacute infarct on NCCT or CTP was considered a true positive if assigned laterality and vascular territory
matched those recorded on DWI. In patients with DWI lesions in more than one vascular territory (including bilateral disease), detection of one lesion by NCCT or CTP was sufficient to be considered as a true positive. The Blyth-Still-Casella procedure was used to construct exact 95% confidence intervals for sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy on NCCT and CTP. An exact McNemar test for the comparison of paired binomial proportions was used to compare the sensitivity, specificity, and overall accuracy of NCCT versus CTP. Generalized estimating equations from a logistic regression model for correlated data were used to compare the predictive values of NCCT versus CTP. All statistical computations were performed on SAS (version 9.0, SAS Institute, Cary, N.C., USA) and StatXact (version 6.0, Cytel Software Corporation, Cambridge, Mass., USA), with p values <0.05 being statistically significant.

**Results**

Patient characteristics are summarized in table 1. Follow-up DWI occurred at a median of 27.5 h (range, 2.0–158) after NCCT and CTP were performed. Thirty-five (35.0%) patients did not have restricted diffusion on follow-up exam to indicate acute infarction. The final discharge diagnoses for these 35 patients were transient ischemic attack in 19 (54.3%), migraine in 3 (8.6%), meningitis in 1 (2.9%), posterior reversible encephalopathy in 1 (2.9%), and undetermined in 11 (31.4%). The 65 (65.0%) patients with hyperacute infarction confirmed on follow-up DWI were distributed in the following vascular territories: 49 in MCA, 8 in PCA, 1 in unilateral MCA and PCA, 1 in bilateral MCA and PCA, and 6 vertebrobasilar.

On NCCT, 17 (26.2%) of the 65 hyperacute infarcts were detected without any false-positive errors. On CTP, 42 (64.6%) of the 65 hyperacute infarcts were detected with one false-positive error (patient with a region of chronic infarction). See figures 1 and 2 for examples of false-negative NCCT and true-positive CTP detections. Of the 23 infarcts that were undetected on CTP, 10 (43.5%) were outside the volume of coverage (territories: 3 in MCA, 1 in PCA, 6 vertebrobasilar). All of the remaining 13 (56.5%) infarcts undetected on CTP were deemed to be within CTP’s coverage and small (including lacunar type) measuring ≤15 mm in maximal dimension. See figure 3 for an example of an acute small infarct missed on CTP.

Section-selective CTP provided 23 (47.9%) additional correct diagnoses of hyperacute infarct for the 48 infarcts undetected on whole-brain NCCT. On the other hand, NCCT did not reveal any of the 23 infarcts that were missed on CTP, but would have corrected for CTP’s single false-positive error of chronic infarction. Diagnostic accuracies of NCCT and CTP are shown in table 2. CTP had significantly better sensitivity (p < 0.0001), negative predictive value (p = 0.032), and overall accuracy (p < 0.0001) than NCCT. CTP was not significantly different from NCCT with respect to specificity or positive predictive value.

**Discussion**

We performed a retrospective study of 100 emergency room patients who presented with an acute neurological deficit within 3 h of onset, were evaluated with NCCT and CTP during triage, and had follow-up DWI to confirm presence or absence of an acute cerebral infarct. Our aim was to determine if diagnostic accuracy can be improved by the additional evaluation of CTP despite its limitation in z-axis coverage of the brain. The results showed that CTP was significantly more sensitive (64.6 vs. 26.2%) and accurate (76.0 vs. 52.0%) than NCCT alone in this critical time window. Nevertheless, 10 infarcts were found outside the CTP coverage volume which represented 15.4% of the 65 confirmed stroke patients in our cohort. Although these 10 infarcts were also undetected on NCCT, it highlights section selectivity as being CTP’s major drawback. The readers were limited by dynamic datasets acquired on a 16-slice CT scanner which provided only 24 mm of z-axis coverage. Youn et al. [16] recently showed that CTP’s detection accuracy can be improved by using 64-slice scanners in combination with the toggling table technique, allowing coverage of up to 80 mm. It is worth noting that the sensitivity for infarcts >15 mm and inside the 24-mm coverage was 100% in our study.

### Table 1. Patient and stroke characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male:female)</td>
<td>53:47</td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>67 (18–96)</td>
</tr>
<tr>
<td>Median NIHSS score (range)</td>
<td>12 (4–28)</td>
</tr>
<tr>
<td>Acute infarct, %</td>
<td>65.0 (65/100)</td>
</tr>
<tr>
<td>Large-vessel infarct, %</td>
<td>69.2 (45/65)</td>
</tr>
<tr>
<td>Small infarct, %</td>
<td>30.8 (20/65)</td>
</tr>
<tr>
<td>Vessel occlusion, %</td>
<td>47.7 (31/65)</td>
</tr>
<tr>
<td>Treated by intravenous tPA, %</td>
<td>38.5 (25/65)</td>
</tr>
<tr>
<td>Recanalization, %</td>
<td>58.3 (14/24)</td>
</tr>
</tbody>
</table>

* Seven patients did not have follow-up angiographic data.
Small hyperacute infarcts, many of the lacunar type, were poorly discernible on both NCCT and CTP, with the latter modality detecting only 2 (15.4%) of the 13 that were within its coverage volume. We attribute this low sensitivity to low signal-to-noise ratio on CT compared to DWI. So while we believe that the sensitivity of CTP for large-vessel infarcts can continue to improve with strategies that increase spatial coverage, small infarcts will likely remain a challenge. We did not exclude small infarcts from our study since they can be important clinically, particularly the lacunar type which have been linked to a class of distinct ‘lacunar syndromes’ [17]. Also, several studies including a subanalysis of the NINDS tPA trial data have shown that all stroke subtypes, including infarcts of small perforating arteries, benefit from thrombolytic therapy [18–20]. We therefore believe that a complete evaluation of a stroke imaging technique must account for lacunar infarcts, which may have in situ or embolic etiologies [21–23].

Fig. 1. A 68-year-old female imaged at 2 h from sudden onset of left hemiparesis. CTA showed no focal arterial stenosis or occlusion (not shown). a NCCT shows no evidence of acute ischemic change. b Map of CBF reveals focal hypoperfusion to the right frontal operculum (arrow). c Map of TTP shows marked prolongation in the same region (arrow). d Map of CBV exhibits subtle low blood volume indicative of infarct (arrow). e DWI at 28.5 h after ictus confirms focal acute infarct in the right frontal operculum (arrow). f Corresponding ADC map of acute infarct (arrow).
Table 2. Diagnostic accuracy of hyperacute infarct <3 h from symptom onset

<table>
<thead>
<tr>
<th>Imaging</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCCT</td>
<td>26.2* (16.2–38.1)</td>
<td>100 (91.2–100)</td>
<td>100 (81.6–100)</td>
<td>42.2* (31.4–53.3)</td>
<td>52.0* (41.8–61.9)</td>
</tr>
<tr>
<td>CTP</td>
<td>64.6* (52.7–76.1)</td>
<td>97.1 (85.3–99.9)</td>
<td>97.7 (88.2–99.9)</td>
<td>59.6* (46.0–72.4)</td>
<td>76.0* (66.9–84.0)</td>
</tr>
</tbody>
</table>

Values are percentages with 95% confidence intervals in parentheses. PPV = Positive predictive value; NPV = negative predictive value. * p < 0.05.

Fig. 2. A 79-year-old female imaged at 1.5 h from sudden onset of mental status change, right hemiparesis, and aphasia. CTA showed a left M1 segment occlusion (not shown). a NCCT shows no signs of acute ischemic change. b Map of CBF reveals severe hypoperfusion to the left caudate, internal capsule, lentiform nucleus, insula cortex, frontal and temporal opercula (arrow). c Map of TTP shows prolongation in most of the left MCA territory (arrow). d Map of CBV exhibits low blood volume indicative of infarct in regions following the distribution of low CBF (arrow). e DWI at 48.5 h following ictus after complete recanalization of the occluded vessel by intra-arterial therapy confirms acute infarct in the areas of hypoperfusion (arrow). f Corresponding ADC map of acute infarct (arrow).
Increased number of false-negatives to our study, but if this had occurred, it was limited to the small infarcts. Patient selection bias may also have affected our results. We examined only patients who had DWI follow-up which excluded 42 (27.8%) of the original 151 patients in the population that presented in the 3-hour window during the inclusion period. Follow-up DWI was a necessary criterion because small infarcts can be difficult to visualize on early follow-up NCCT [24]. Doing so also allowed us to select a cohort that carried a uniform reference standard. Finally, in regard to disease prevalence in our retrospective cohort, acute infarction was present in 65% of patients which compares favorably to a recent large prospective study in which the prevalence of an acute ischemic infarct was 62% in those who arrived in the 3-hour window with sudden neurological deficit [1].

The results of this study may provide compelling reasons why CTP should be performed in the 3-hour window. We believe, as do others [1], that greater accuracy for acute stroke should logically result in an increased number of patients being treated since more of them will be confidently diagnosed at triage. While NCCT is adequate
for those patients who have a high pretest probability, the cases in which there is diagnostic uncertainty will result in delay or nontreatment. For example, Barber et al. [25] have shown in their large cohort study that nearly a third of patients who arrived within the 3-hour window but were not given tPA because of ‘improving’ symptoms (presumed transient ischemic attack) were left disabled or died during the hospital admission. A more definitive diagnosis of acute stroke also allows the stroke team to better initiate and apply hospital resources (e.g. admission to intensive care facility/unit). Finally, NCCT usually provides little information regarding vessel status which can be critical since an ICA terminus or M1 clot is critical than it is for patient presentation beyond the first 3 h when a justification is needed for off-label usage of intravenous tPA. Such was the motivation behind our study of whether CTP improves stroke detection during this early time frame when the key to favorable patient outcome remains early diagnosis and treatment [30].

We did not delve into the issue of salvageable tissue at risk (‘penumbra’) even though it is the primary target of perfusion stroke imaging [26–29]. We believe, as do others [30], that in the 3-hour window, it is most important to determine whether acute ischemia is present that requires intervention. The question of penumbra is less critical than it is for patient presentation beyond the first 3 hours.

References


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