

Acute Brain Infarct: Detection and Delineation with CT Angiographic Source Images versus Nonenhanced CT Scans¹

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Purpose:

To retrospectively compare sensitivity and specificity of admission nonenhanced computed tomographic (CT) scans with those of CT angiographic source images in detection of early ischemic changes in middle cerebral artery (MCA) stroke and to retrospectively compare admission nonenhanced CT scans with CT angiographic source images in delineation of final infarct extent, with follow-up images as reference.

Materials and Methods:

Informed consent and institutional review board approval were received for this HIPAA-compliant study. Nonenhanced scans and angiographic source images obtained within 12 hours of symptom onset in 51 patients suspected of having MCA stroke were reviewed. Two blinded neuroimagers rated presence and extent of hypoattenuation on nonenhanced scans and angiographic source images with Alberta Stroke Programme Early CT Score (ASPECTS). Level of certainty for hypoattenuation detection was assigned a grade with a five-point scale. With receiver operating characteristic (ROC) curve analysis, nonenhanced scans and angiographic source images were compared for stroke detection. For stroke delineation, linear regression coefficients determined correlations of ASPECTS for nonenhanced scans and angiographic source images with ASPECTS for follow-up images. Multiple linear regressions were used to compare these correlations.

Results:

Follow-up nonenhanced CT scans, diffusion-weighted magnetic resonance (MR) images, or fluid-attenuated inversion-recovery MR images were obtained (mean time to follow-up, 5.4 days); 33 patients had infarction. With level of certainty cutoff score of 4 or greater (probable, definite) for ischemic hypoattenuation, sensitivity for detection of acute stroke was 48% (nonenhanced scans) and 70% (angiographic source images) ($P = .04$, ROC analysis); specificity was 100% for both. Linear regression revealed $R^2 = 0.42$ ($P < .001$) for correlation between delineation of stroke on nonenhanced scans and on follow-up images evaluated with ASPECTS and 0.73 ($P < .001$) for correlation between delineation on angiographic source images and follow-up images evaluated with ASPECTS ($P < .001$, nonenhanced scans vs angiographic source images).

Conclusion:

CT angiographic source images, compared with nonenhanced CT scans, are more sensitive in detection of early irreversible ischemia and more accurate for prediction of final infarct volume.

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The Alberta Stroke Programme Early CT Score (ASPECTS) is an established scale for quantifying hypoattenuation from acute stroke on non-enhanced computed tomographic (CT) scans and helps in the prediction of clinical outcome (1,2). ASPECTS has been used as a reliable and convenient surrogate for visual interpretation of lesion volume not only on nonenhanced CT scans but also on CT angiographic source images and diffusion-weighted magnetic resonance (MR) images (3–6). Unlike other forms of perfusion imaging, CT angiographic source images cover the entire brain, do not rely on the interpretation of nonenhanced images, do not require postprocessing, and are available immediately at completion of imaging.

Given these results, as well as our clinical experience, we hypothesized that the sensitivity of CT angiographic source images for both the detection and delineation of acute ischemic lesions would substantially exceed that of nonenhanced CT scans. This benefit is especially important at early acute stroke time frames when nonenhanced CT hypoattenuation is not established yet urgent treatment decisions are warranted for optimal patient care. Although data in earlier work have suggested that this is likely to be the case for determination of extent of the lesion—but not detection rate—the reported effect was modest, in part attributable to the clinical severity of stroke in the cohort studied (median National Institutes of Health Stroke Scale [NIHSS] score, 16). These factors tended to minimize the dif-

ference between the nonenhanced and enhanced CT findings (5).

The purpose of our study was to retrospectively compare the sensitivity and specificity of admission nonenhanced CT scans with those of CT angiographic source images in the detection of early ischemic changes in middle cerebral artery (MCA) stroke and to retrospectively compare admission nonenhanced CT scans with CT angiographic source images in the delineation of final infarct extent, by using follow-up images as the reference standard.

Materials and Methods

We analyzed data from 110 consecutive patients enrolled in a prospective cohort study at two university-based hospitals, part of the Screening Technology and Outcomes Project in Stroke (also known as STOPStroke), at which emergency CT angiography for patients suspected of having ischemic stroke (stroke, transient ischemic attack, or stroke mimics) was performed. In the Screening Technology and Outcomes Project in Stroke, admission nonenhanced CT scans were obtained in all subjects, followed by acquisition of CT angiograms and CT angiographic source images. Patients were excluded if iodinated contrast agent administration was contraindicated (ie, history of contrast agent allergy, pregnancy, congestive heart failure, increased creatinine level) or if there was evidence of intracranial hemorrhage on nonenhanced CT scans.

The prospective Screening Technology and Outcomes Project in Stroke study and our current retrospective study received institutional review board approval at both participating institutions and were Health Insurance Portability

and Accountability Act compliant. At enrollment for the prospective study, all subjects gave informed consent for participation in both the prospective study and any future retrospective studies by using the Screening Technology and Outcomes Project in Stroke data information.

In the participating hospitals, CT angiography is always performed urgently for patient care and decision making in regard to thrombolytic treatment. However, because CT angiographic data were not the focus of our current cohort examination, they were not included in the analysis.

Within our cohort, 82 patients had signs and symptoms suggestive of MCA territory stroke and were enrolled in the study from March through August 2003. Of these, 51 patients who were imaged within 12 hours of symptom onset and who did not have evidence of old strokes on admission nonenhanced CT scans were included in the study. Mean patient age was 64.3 years (range, 21–96 years); 53% (27) were women and 47% (24) were men.

Neuroimaging Protocol

Acute stroke CT angiographic protocol.—Nonenhanced CT and CT angiographic acquisitions were performed according to standard departmental protocols with eight- or 16-section multidetector CT

Advance in Knowledge

- CT angiographic source images, compared with nonenhanced CT scans, are more sensitive in the detection of early irreversible ischemia (70% vs 48% sensitivity, respectively, $P = .04$) and more accurate in the prediction of final infarct volume, by using evaluation with ASPECTS (correlation to final infarct ASPECTS: $R^2 = 0.73$ for CT angiographic source images and 0.42 for nonenhanced CT scans).

Implication for Patient Care

- Through enabling more sensitive detection of stroke and more accurate prediction of final infarct extent, CT angiographic source images provide clinicians with useful information about stroke severity, which may influence patient treatment.

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Abbreviations:

ASPECTS = Alberta Stroke Programme Early CT Score
CI = confidence interval
MCA = middle cerebral artery
NIHSS = National Institutes of Health Stroke Scale
ROC = receiver operating characteristic

Author contributions:

Guarantors of integrity of entire study, K.L.F., W.J.K., M.H.L.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, E.C.S.C., W.J.K., M.H.L.; clinical studies, E.C.S.C., K.L.F., A.B.S., L.R., M.E.C., W.S.S., W.J.K., M.H.L.; statistical analysis, E.C.S.C., E.F.H., M.H.L.; and manuscript editing, E.C.S.C., K.L.F., A.B.S., L.R., G.J.H., W.S.S., W.J.K., M.H.L.

scanners (LightSpeed; GE Healthcare, Milwaukee, Wis) (7,8).

Nonenhanced CT was performed, with the patient in a head holder, in the transverse plane. Representative sample parameters, with minimal variations between scanners and sites shown as ranges, were as follows: 120–140 kVp, 170 mA, 2-second scan time, and 5-mm section thickness. Imaging with these parameters was immediately followed by biphasic helical scanning, performed at the same head tilt as was nonenhanced CT. CT angiography was performed after a 25-second delay (40 seconds for patients in atrial fibrillation) and administration of 100–140 mL of a nonionic contrast agent (Isovue; Bracco Diagnostics, Princeton, NJ) at an injection rate of 3 mL/sec by using a power injector (Medrad Power Injector; Medrad, Indianola, Pa) via an 18-gauge intravenous catheter. Parameters were 140 kVp, 220–250 mA, 0.8–1.0-second rotation time, 2.5-mm section thickness, 1.25-mm reconstruction interval, 3.75 mm per rotation table speed, and 0.75:1 pitch. Images were obtained from the C6 vertebral body level through the circle of Willis. Immediately afterward, a second set of images was obtained from the aortic arch to the skull base. Afterward, source images were reconstructed into standardized maximum intensity projection views of the intracranial and extracranial vasculature.

Follow-up neuroimaging as reference standard.—All patients underwent follow-up neuroimaging studies within 10 days after stroke onset. The patients' treating physicians decided timing of follow-up imaging and the imaging modality to be used. When more than one appropriate follow-up image was available, an independent rater, who was not involved in assigning grades to the admission nonenhanced CT scans and CT angiographic source images, selected for inclusion the follow-up image that most clearly confirmed the presence or absence of a new ischemic stroke. When available, preference was given to diffusion-weighted MR images, followed by fluid-attenuated inversion-recovery MR images, and finally nonenhanced CT scans.

The criteria used to define the presence or absence of an ischemic stroke on

follow-up images were as follows: (a) for nonenhanced CT scans, low-attenuation regions in the MCA territory that were not suggestive of encephalomalacia and/or chronic infarction on the admission nonenhanced CT scans; (b) for diffusion-weighted MR images, hyperintense regions in the MCA territory, with corresponding restricted diffusion on the apparent diffusion coefficient maps; and (c) for fluid-attenuated inversion-recovery MR images, hyperintense regions in the MCA territory that were also not suggestive of chronic infarct and that corresponded to regions of restricted diffusion on the admission apparent diffusion coefficient maps.

Nonenhanced CT was performed by using the same protocol as was described previously. MR imaging was performed with a 1.5-T unit with echo-planar capabilities (Signa; GE Healthcare). Diffusion-weighted MR imaging acquisition parameters were as follows: repetition time msec/echo time msec, 7500/73; low b value, 0 sec/mm² (rounded to the nearest 0.01); high b value, 1000 sec/mm²; gradient directions, six; number of signals acquired, one; matrix, 128 × 128; acquisition time, approximately 3 minutes. Transverse fluid-attenuated inversion-recovery MR images were obtained with repetition time msec/echo time msec/inversion time msec, 10 002/141/2200; field of view, 24 cm; acquisition matrix, 256 × 192 pixels; section thickness, 5 mm, with a 1-mm gap; number of signals acquired, one; and acquisition time, approximately 4 minutes.

Image Review

Image review was independently performed on a picture archiving and communication system workstation (Impax; Agfa Technical Imaging Systems, Richfield Park, NJ) by a board-certified neuroradiologist and a clinical neurologist experienced in stroke neuroimaging interpretation (M.H.L. and W.J.K., 15 and 25 years of neuroimaging review experience, respectively). Reviewers were blinded to follow-up clinical and imaging findings but had information in regard to the patients' age, sex, and presenting clinical symptoms. Neither of the reviewers had participated in the selection of the patients.

Variable window width and center level settings were used for optimal ischemic hypoattenuation detection with nonenhanced CT and CT angiographic source images (9). In all cases, nonenhanced CT images obtained for acute stroke were reviewed first, followed by CT angiographic source images, and finally, follow-up images for confirmation of true-positive or true-negative infarct regions. Disagreements in readings were resolved in consensus.

Reviewers rated the ischemic lesion on the nonenhanced CT scans, CT angiographic source images, and follow-up images according to ASPECTS (10). Therefore, for every image, we reviewed each of 10 regions for the presence or absence of ischemic lesions according to a five-point level of certainty score (score 5, definitely present; score 4, probably present; score 3, equivocal; score 2, probably absent; score 1, definitely absent). These regions included the insula (I), caudate nucleus (C), lentiform nucleus (L), internal capsule (IC), superior parietal lobe (M6), precentral and superior frontal lobe (M5), anterior superior frontal lobe (M4), inferior parietal and posterior temporal lobe (M3), temporal lobe (M2), and anterior inferior frontal lobe (M1).

In addition, final infarct volumes were segmented from the follow-up images. The follow-up images were transferred to a personal computer (P4S533-E; Asus, Taipei, Taiwan) and processed with an image analysis software package (Analyze; Mayo Foundation for Medical Education and Research, Rochester, Minn). Segmented regions of interest were drawn around the final infarct by an investigator who was blinded to the admission scan findings. Care was taken to exclude regions of volume averaging that included adjacent cerebrospinal fluid spaces.

Statistical Analysis

Stroke detection.—To compare stroke detection rates with nonenhanced CT and CT angiographic source images, we used standard receiver operating characteristic (ROC) curve analysis methods (Rockit 0.9B, beta version, 1998; University of Chicago, Chicago, Ill) (11). For input to

the ROC program, because the presence of even a single low-attenuation ischemic lesion implies the presence of stroke, we chose the highest level of certainty score (ie, the highest rated level of certainty score for the presence of stroke) of the 10 regions from each image that were rated with ASPECTS. The standard for the presence or absence of stroke was determined by using follow-up images. ROC analyses were performed separately for nonenhanced CT scans and CT angiographic source images, and the optimal operating points (ie, level of certainty scores that had the best corresponding areas under the curve) for each imaging modality were chosen. A difference with $P < .05$ was considered significant. Sensitivity, specificity, and accuracy for nonenhanced CT scans and CT angiographic source images, with different level of certainty scores, were recorded.

Stroke delineation.—Totals for the ASPECTS were calculated for the nonenhanced CT scans, CT angiographic source images, and follow-up images by deducting one point for each territory with abnormal ASPECTS from a maximal normal score of 10; level of certainty scores of 3, 4, or 5 were considered abnormal. Stan-

dard linear regression coefficients were calculated to determine the correlation of each of the nonenhanced CT scan and CT angiographic source image ASPECTS with follow-up image ASPECTS, by using level of certainty cutoff scores of 3 and 4. Comparison of the correlations of nonenhanced CT scan and CT angiographic source image ASPECTS with follow-up image ASPECTS, for each level of certainty cutoff score, was based on the type III sums of squares in a multiple linear regression model. A difference with $P < .05$ was considered significant. Software (SAS 9.1, 2002–2003; SAS Institute, Cary, NC) was used for the calculations.

Standard linear regression coefficients were also calculated to determine the correlation of each of the nonenhanced CT scan and CT angiographic source image ASPECTS with final infarct volumes on follow-up images by using the optimal level of certainty cutoff score. Comparison of the correlations of nonenhanced CT scan and CT angiographic source image ASPECTS with follow-up image volume was based on the type III sums of squares in a multiple linear regression model. A difference with $P < .05$ was considered significant. Software (SAS 9.1, 2002–2003; SAS Institute) was used for the calculations.

ment occlusions, and nine had M2 MCA segment occlusions. No other arterial occlusions were detected in the remaining 11 patients with stroke.

Mean time from symptom onset to nonenhanced CT was 7.2 hours, mean interval between acquisition of nonenhanced CT scans and CT angiographic source images was 6 minutes, and mean time to follow-up study was 5.4 days. The breakdown in time to follow-up according to modality was as follows: For diffusion-weighted MR imaging performed in 38 subjects, the range was 1.4–54 hours for patients without stroke and normal findings at clinical presentation at the time of initial scanning and 3.8 hours to 5.7 days for patients with stroke. For nonenhanced CT performed in eight patients, the range was 20.4 hours to 9.9 days. For fluid-attenuated inversion-recovery MR imaging performed in five patients, the range was 4.9–8.7 days. Ten patients received thrombolytic therapy: Four received therapy with intravenous recombinant tissue plasminogen activator. Six patients received therapy with intraarterial mechanical or chemical thrombolysis; in two of the six patients, recanalization was successful.

Figure 1

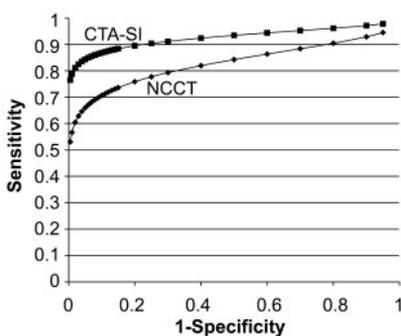


Figure 1: ROC curves show sensitivity and specificity values for infarct core detection with nonenhanced CT scans (NCCT) and CT angiographic source images (CTA-SI) at various level of certainty cutoff scores, as described in the Methods section. With a level of certainty cutoff score of 4 or greater (probable, definite) for the presence of any acute ischemic hypoattenuation, overall accuracy for stroke detection was 0.66 with nonenhanced CT scans (95% confidence interval [CI]: 0.60, 0.95) and 0.80 (95% CI: 0.72, 0.99) with CT angiographic source images.

Results

Follow-up images revealed that 18 patients were without infarction; 33 patients had MCA territory strokes. Among these 33 patients, 17 (52%) had a cardioembolic stroke, one (3%) had a stroke that involved a large vessel, four (12%) had a stroke that involved a small vessel, six (18%) had a cryptogenic stroke, and five (15%) had a stroke that was classified as other (one with polyarteritis nodosa, one that occurred after carotid endarterectomy, one with arterial dissection, one associated with cocaine use, and one associated with neoplasia). The median admission NIHSS score was 5 (mean, 7.7; range, 0–31). Of the 33 patients with stroke, one had a top of the internal carotid artery “T” lesion, three had internal carotid artery and M1 MCA segment occlusions, seven had M1 MCA segment occlusions, two had M1 and M2 MCA seg-

Stroke Detection

With a level of certainty cutoff score of 4 or greater (probable, definite) for the presence of any acute ASPECTS template ischemic hypoattenuation, stroke detection sensitivity was 48% (16 of 33) with nonenhanced CT scans and 70% (23 of 33) with CT angiographic source images, with a two-sided test that was based on ROC curves ($P = .04$); specificity was 100% with both types of images (Fig 1). For the same cutoff score, overall accuracy for stroke detection was 0.66 (34 of 51) with nonenhanced CT scans (95% CI: 0.60, 0.95) and 0.80 (41 of 51) with CT angiographic source images (95% CI: 0.72, 0.99). With a level of certainty cutoff score of 3 or greater (possible, probable, and definite) for the presence of any acute ischemic hypoattenuation, sensitivity was 64% (21 of 33) with nonenhanced CT scans and 85% (28 of 33) with CT angiographic source images, with a two-sided test that was based on ROC curves ($P = .02$); specificity was minimally re-

Figure 2

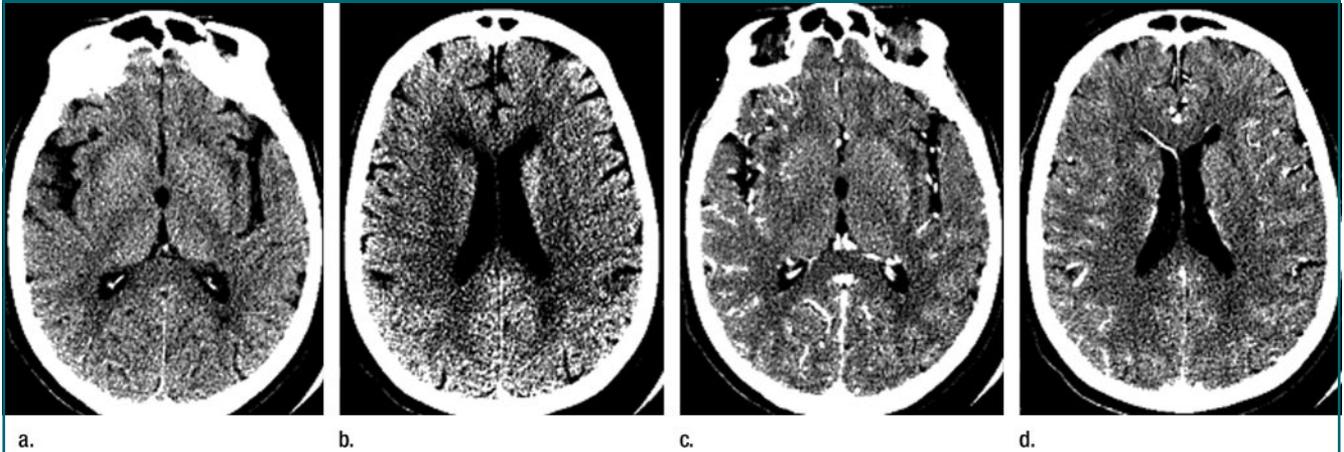


Figure 2: Imaging findings in a 71-year-old left-handed woman with a history of malignancy and smoking, who presented 75 minutes after acute onset of left hemiplegia, left hemisensory loss, and profound neglect (NIHSS score, 19). (a, b) Transverse nonenhanced CT scans and (c, d) CT angiographic source images are without definite early ischemic hypoattenuation.

Figure 3

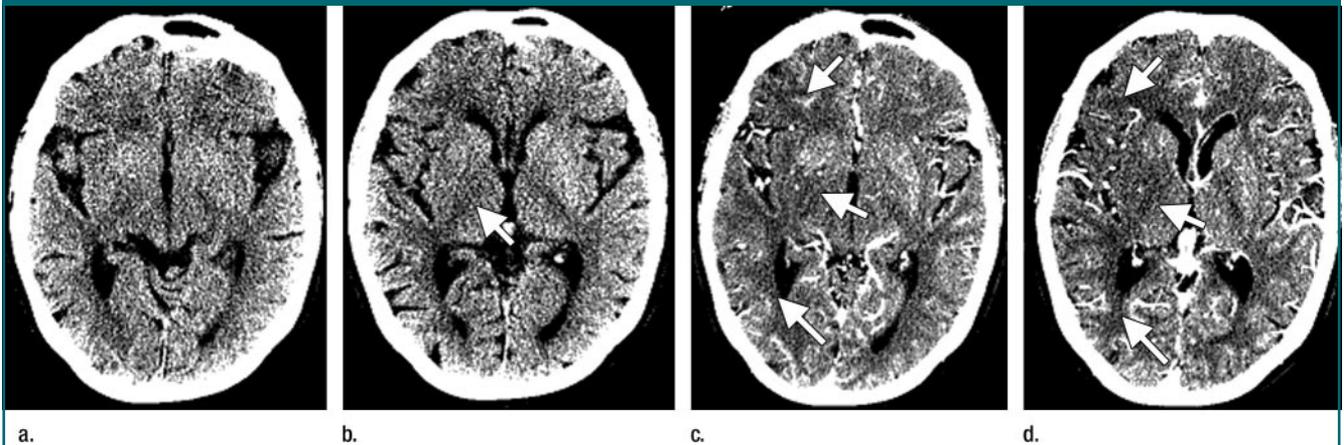


Figure 3: Imaging findings in a 72-year-old woman with history of hypertension and atrial fibrillation who presented with acute left hemiparesis, mild left hemisensory loss, neglect, and dysarthria (NIHSS score, 11). Neuroimaging was performed 4.5 hours after onset. (a, b) Transverse nonenhanced CT scans demonstrate only minimal subtle hypoattenuation of the right lentiform nucleus (arrow), as assessed by both neuroimaging reviewers. (c, d) Transverse CT angiographic source images reveal more conspicuous and widespread low attenuation, delineating more accurately hypoattenuation of the right lentiform nucleus, as well as of the right insula, superior and posterior temporal lobe, and inferior parietal lobe (arrows).

duced to 89% (16 of 18) with nonenhanced CT scans and 94% (17 of 18) with CT angiographic source images (Figs. 2–4).

Stroke Delineation

On the basis of the ROC analysis, level of certainty scores of 4 or greater (probable and definite) and of 3 or greater (possible, probable, and definite) were chosen as optimal operating points. With the cut-off scores of 3 or greater and of 4 or

greater as positive for the presence of acute ischemic lesion, ASPECTS was computed for all images. Only one patient had a minimally higher ASPECTS on follow-up images than on admission nonenhanced CT scans and CT angiographic source images (ASPECTS of 9, 8, and 6, respectively, with a cutoff score of ≥ 4).

For a cutoff score of 4 or greater, linear regression analysis revealed an $R^2 = 0.42$ ($P < .001$; slope = 1.53; 95% CI: 1.01, 2.05) for correlation between

admission nonenhanced CT scan ASPECTS and follow-up image ASPECTS (Fig 5) and an $R^2 = 0.73$ ($P < .001$; slope = 1.11; 95% CI: 0.91, 1.30) for correlation between admission CT angiographic source image ASPECTS and follow-up image ASPECTS (Fig 6). On the basis of a stepwise multiple regression analysis, CT angiographic source images showed significant improvement in the determination of the ASPECTS with follow-up images compared with determina-

tion with nonenhanced CT scans ($P < .001$). The reverse, however, was not true, as nonenhanced CT scans did not significantly add value to CT angiographic source images in the same model.

For a cutoff score of 3 or greater, linear regression analysis revealed an $R^2 = 0.41$ ($P < .001$; slope = 1.02; 95% CI: 0.67, 1.38) for correlation between admission nonenhanced CT scan ASPECTS and follow-up image ASPECTS and an $R^2 = 0.68$ ($P < .001$; slope = 0.95;

95% CI: 0.77, 1.15) for correlation between admission CT angiographic source image ASPECTS and follow-up image ASPECTS. For the cutoff level of certainty of 3 or greater, CT angiographic source images did not significantly improve stroke delineation compared with nonenhanced CT scans in the stepwise multiple regression analysis.

In addition, to compare the performance of nonenhanced CT scans versus that of CT angiographic source images for

stroke delineation, we correlated the nonenhanced CT and CT angiographic source image ASPECTS (by using a cutoff level of confidence of ≥ 4 , which was previously determined as optimal) to final infarct volume. This linear regression analysis revealed an $R^2 = 0.26$ ($P < .001$) for correlation between admission nonenhanced CT scan ASPECTS and follow-up image infarct volume and an $R^2 = 0.43$ ($P < .001$) for correlation between admission CT angiographic source image

Figure 4

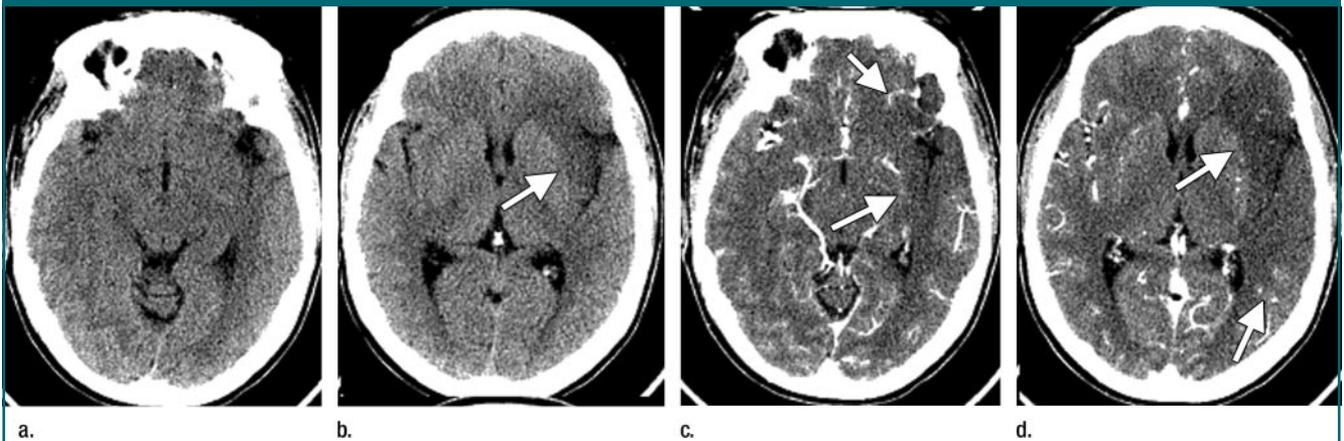


Figure 4: Imaging findings in a 46-year-old diabetic woman who presented with sudden onset of right hemiparesis, global aphasia, and gaze deviation (NIHSS score, 13). (a, b) Transverse nonenhanced CT scans obtained 10 hours after stroke onset demonstrate hypoattenuation of the left insula only (arrow). (c, d) Transverse CT angiographic source images help improve detection and delineation of other infarcted regions, including left anterior and posterior temporal lobe, inferior parietal lobe, and inferior frontal lobe (arrows).

Figures 5, 6

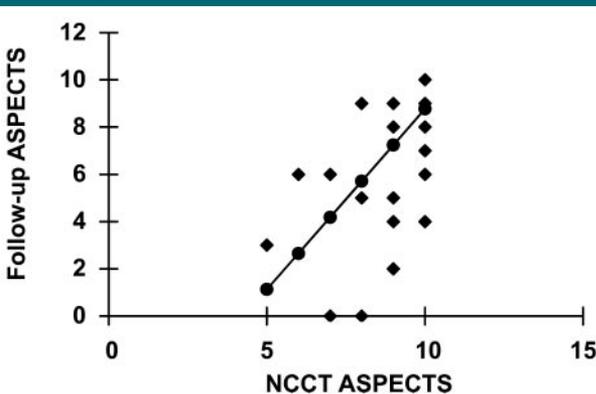


Figure 5: Linear regression between admission nonenhanced CT scan (NCCT) and follow-up image ASPECTS at a level of certainty cutoff score of 4 for hypoattenuating lesion delineation ($R^2 = 0.42$; $P < .001$; slope, 1.53; 95% CI: 1.01, 2.05). \blacklozenge = Follow-up image ASPECTS, \bullet = predicted follow-up image ASPECTS.

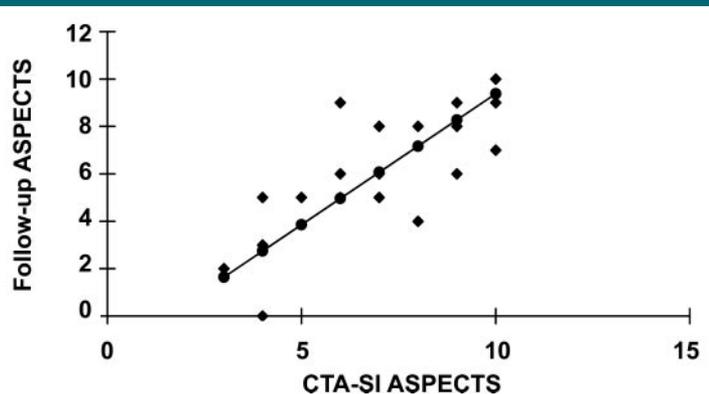


Figure 6: Linear regression between admission CT angiographic source image (CTA-SI) and follow-up image ASPECTS at a level of certainty cutoff score of 4 for hypoattenuating lesion delineation ($R^2 = 0.73$; $P < .001$; slope, 1.11; 95% CI: 0.91, 1.30). \blacklozenge = Follow-up image ASPECTS, \bullet = predicted follow-up image ASPECTS.

ASPECTS and follow-up image infarct volume. On the basis of a stepwise multiple regression analysis, CT angiographic source images were more strongly correlated with final infarct volume than were nonenhanced CT scans ($P < .001$). Conversely, nonenhanced CT scans did not significantly add value to CT angiographic source images as an independent predictor of final infarct volume in the same model.

Discussion

Our results show that, in this selected population, CT angiographic source images were both (a) more sensitive than nonenhanced CT scans in the early detection of irreversible MCA infarction within 12 hours of symptom onset, without sacrifice of specificity, and (b) more accurate than nonenhanced CT scans in delineation of final infarct extent, as measured by using ASPECTS. Findings in earlier work have suggested that CT angiographic source images may have added value compared with nonenhanced CT scans (5). Our findings expand on previous results with the use of ROC methods and with the study of a less severely affected patient population, both of which can bring out the subtle differences between CT angiographic source images and nonenhanced CT scans in our patient population.

These findings underscore the potentially important role of both vascular CT angiograms (useful in triaging patients to intraarterial treatments) and parenchymal CT angiographic source images (a free bonus when vascular CT angiograms are obtained) in acute stroke evaluation (12,13). It has been suggested that the combination of vascular CT angiograms with parenchymal CT angiographic source images, compared with admission nonenhanced CT scans alone, improves the overall accuracy of infarct localization, vascular territory determination, vessel occlusion identification, stroke subtyping, and prediction of final stroke extent (1,14). There may be additional advantages with dynamic perfusion images, which can be obtained subsequent to CT angiographic source images and which delineate regions that are ische-

mic but not yet infarcted at admission (15).

Findings in previous studies in which the researchers used conventional ASPECTS have indicated a less robust benefit of CT angiographic source images compared with nonenhanced CT scans in the prediction of final infarct extent (5). Our study results expand on data in earlier work by comparing the detection of acute ischemic hypoattenuation with nonenhanced CT scans versus CT angiographic source images by means of ROC analysis, with the use of a level of certainty score for rating the detection of more subtle ischemic change than is possible with an all-or-none or present-or-absent approach (5). Indeed, the use of a level of certainty score makes possible the application of ROC methods.

Other details of our study also differ from those of earlier work (5). Our study has a large sample size, with a relatively low median admission NIHSS score; 35% of patients did not have stroke, which was confirmed by using follow-up imaging; and there was a longer mean time from symptom onset to nonenhanced CT scanning—potentially leading to an exaggeration of the difference between subtle or equivocal ischemic areas of hypoattenuation on the nonenhanced and enhanced images. In the study by Coutts et al (5), the median admission NIHSS score was 16; hence, their patient population should have had more marked early ischemic changes on the initial nonenhanced CT scans. This would diminish the advantage of CT angiographic source images compared with nonenhanced CT scans in the detection of, but not in the delineation of, ischemic changes. In addition, as our study was part of an ongoing multicenter investigation, readers were trained specifically for evaluation of ischemic hypoattenuation with ASPECTS, which may have contributed to the consistency and uniformity of our results.

Researchers in other studies have suggested that lesion volume on admission CT angiographic source images strongly correlates with final infarct volume in MCA stroke patients with early complete recanalization (slope, approximately 1), and, hence, like diffusion-weighted MR images, provides a measure

of infarct core (tissue likely to be irreversibly damaged despite major reperfusion) (2,14,16). Although it is clear that the sensitivity of diffusion-weighted MR images far exceeds that of CT angiographic source images for the detection of small punctate lacunar and distal embolic infarcts, it has been suggested that for larger infarcts—those which may influence the decision to perform thrombolytic treatment—the sensitivity of CT angiographic source images approaches that of diffusion-weighted images (14,16,17).

Moreover, CT angiography with CT angiographic source images is typically more available, faster, affordable, and easier to perform in critically ill patients than is MR imaging (7,12). When used in conjunction with quantitative first-pass CT perfusion images, which provide a measure of penumbral tissue at risk, CT angiographic source images compared with CT perfusion images for ischemic lesion size mismatch have the potential to aid in the selection of patients for treatments in a manner analogous to diffusion-weighted MR images compared with perfusion images for mismatch. In the Desmoteplase in Acute Ischemic Stroke (known as DIAS) (18) and Diffusion-Weighted Imaging Evaluation for Understanding Stroke Evolution (called DEFUSE) (19) trials, MR imaging mismatch was employed to safely and effectively select patients for intravenous thrombolytic therapy beyond a strict 3-hour time window.

Major limitations of our investigation relate largely to technical issues that involve CT scanning, and these include beam-hardening and other artifacts, the confounding effects of preexisting hypoattenuation caused by chronic stroke or white matter disease, and the limited capability of CT for the detection of small areas of infarction caused by intrinsic image noise (2). In addition, we did not control for treatment, which could have influenced final infarct extent in selected cases. Nonetheless, only one patient had a higher ASPECTS on follow-up images than on admission nonenhanced CT scans and CT angiographic source images, so it is unlikely that treatment appreciably reversed final infarct extent. Even had treatment altered infarct volume on follow-up

images, however, it would be unlikely to have influenced detection rates for infarcts.

Also, because nonenhanced CT readout was performed prior to CT angiographic readout, this difference may have biased the detection of ischemic hypoattenuation with CT angiographic source images, as readers were aware of the presence or absence of intra- and extracranial arterial occlusions when they rated the CT angiographic source images. This was a conscious intention of our study design, however, as the order of readout was chosen to simulate the actual clinical scenario in which the nonenhanced CT scans are reviewed first. Indeed, the fact that readers were aware of pertinent presenting signs and symptoms when they were interpreting the nonenhanced CT scans clearly influenced the pretest probability that a given hypoattenuation was real or artifactual, although this knowledge should have affected the nonenhanced CT scan and CT angiographic source image readouts equally. Again, awareness of the clinical history was intended to simulate the clinical setting, and, if anything, the bias is toward favoring nonenhanced CT scan sensitivity, as previous work has shown that knowledge of the emergency clinical findings at presentation improves detection of stroke with nonenhanced CT scans (but not with diffusion-weighted MR images) (20).

In conclusion, the results of our study support the role of CT angiographic source images, rather than nonenhanced CT scans alone, in improving both the detection of early ischemic changes and the prediction of final infarct extent and, hence, favor the use of CT angiography and CT angiographic source images in the emergency setting for diagnosis and triage of patients with potential stroke.

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