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Can the Ischemic Penumbra Be Identified on Noncontrast CT of Acute Stroke?

Keith W. Muir, MD, FRCP; Jonathan Baird-Gunning, BSc; Leighton Walker, FRCR; Tracey Baird, MRCP; Michael McCormick, MRCP; Shelagh B. Coutts, MD, FRCPC

Background and Purpose—Early ischemic changes on noncontrast CT in acute stroke include both hypoattenuation and brain swelling, which may have different pathophysiological significance.

Methods—Noncontrast CT and CT perfusion brain scans from patients with suspected acute stroke <6 hours after onset were reviewed. Five raters independently scored noncontrast CTs blind to clinical data using the Alberta Stroke Program Early CT Score (ASPECTS). Each ASPECTS region was scored as hypodense or swollen. A separate reviewer measured time to peak and cerebral blood volume in each ASPECTS region on CT perfusion. Time to peak and cerebral blood volume were compared for each region categorized as normal, hypodense, or isodense and swollen.

Results—Scans of 32 subjects a median 155 minutes after onset yielded 228 regions with both CT perfusion and noncontrast CT data. Isodense swelling was associated with significantly higher cerebral blood volume ($P=0.016$) and with penumbral perfusion (posttest:pretest likelihood ratio 1.44 [95% CI: 0.68 to 2.90]), whereas hypodensity was associated with more severe time to peak delay and with core perfusion (likelihood ratio 3.47 [95% CI: 1.87 to 6.34]). Neither isodense swelling nor hypodensity was sensitive for prediction of perfusion pattern, but appearances were highly specific (87.2% and 91.0% for penumbra and core, respectively). Intrarater agreement was good or excellent, but interrater agreement for both hypodensity and swelling was poor.

Conclusions—Regions exhibiting hypoattenuation are likely to represent the infarct core, whereas regions that are isodense and swollen have increased cerebral blood volume and are more likely to signify penumbral perfusion. Although noncontrast CT is not sensitive for detection of core and penumbra, appearances are specific. Some information on tissue viability can therefore be obtained from noncontrast CT. (*Stroke*. 2007;38:2485-2490.)

Key Words: acute stroke ■ computed tomography ■ diagnosis ■ perfusion CT ■ perfusion imaging

Early ischemic changes (EICs) on noncontrast CT (NCCT) of the brain include changes in brain parenchyma that reflect either decreased attenuation (eg, loss of definition of the lentiform nucleus) or tissue swelling (eg, hemispheric sulcal effacement, effacement of the lateral ventricle).^{1,2} Early ischemic changes are present in 60% to 80% of NCCT scans within 3 hours of middle cerebral artery occlusion in clinical trials of thrombolysis.^{3–5} Systematic approaches to recognition of EIC such as the Alberta Stroke Program Early CT Score (ASPECTS) system improve the detection of EIC.^{3–6} However, neither ASPECTS nor other descriptive approaches distinguish clearly between hypodensity (hypoattenuation) and brain swelling, which may have different underlying pathophysiology.⁷

Hypodensity on NCCT is probably caused by increased net water uptake⁸ and corresponds to severe ischemia that is likely to result in infarction.^{9–13} Decreased attenuation

on NCCT correlates with the apparent diffusion coefficient value on diffusion-weighted MRI¹⁰ with the visualized diffusion-weighted MRI lesion,¹⁴ with reduced cerebral blood flow on positron emission tomography,^{9,15} and also with reduced cerebral blood flow and cerebral blood volume (CBV) derived from perfusion MRI.^{7,11} Methods of assessing brain perfusion using contrast-enhanced CT such as the use of CT angiography source images^{16,17} or CT perfusion source images (CTP-SI)^{18,19} increase the sensitivity of CT for identification of ischemic lesions and rely on increased contrast between tissue with preserved, and tissue with decreased, CBV. Lesions identified from CT angiography source images correspond to those on diffusion-weighted MRI.¹⁶

The response of metabolically active tissue to reduced cerebral perfusion pressure is autoregulatory vasodilatation to maintain cerebral blood flow.^{20,21} This results in increased

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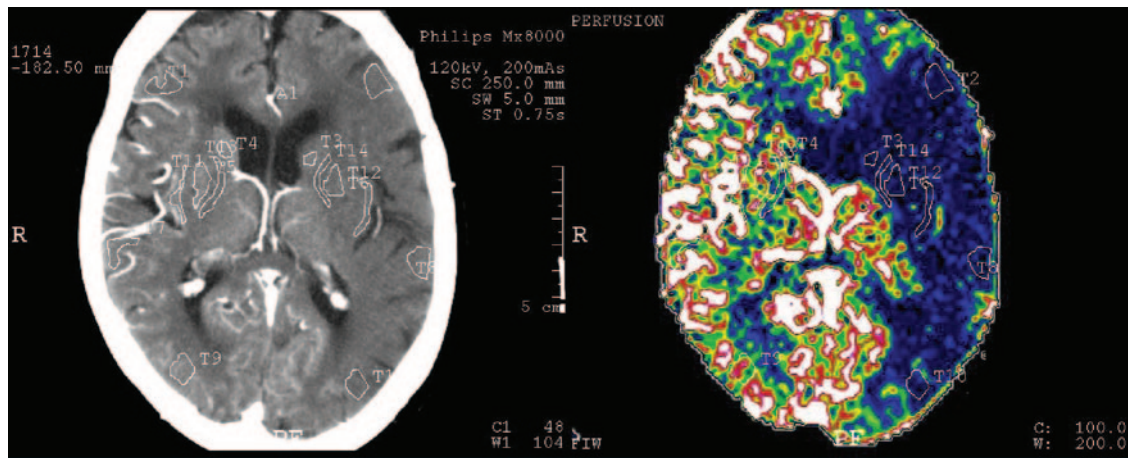
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ASPECTS Region	TTP (secs)		CBV	
	R	L	R	L
M1	7.4	16.3	90.2	10.0
Caudate	6.1	21.5	114.9	8.1
Lentiform	6.9	16.6	118.8	11.9
M2	7.2	11.9	104.5	11.6
M3	8.6	20.9	149.0	35.1
Insula	6.1	16.5	109.8	16.4

Figure 1. Example of regions of interest drawn on a the maximum intensity projection image of the perfusion CT scan with corresponding CBV map and TTP and CBV measurements from each region.

CBV in tissue that retains metabolic capacity. Increased CBV on MR perfusion scans acquired within a short time of NCCT has been reported in association with regions of isodense swelling.^{7,22}

We sought to verify the hypothesis that hypodensity and swelling without hypodensity on NCCT in acute stroke have different pathophysiological significance by using CT perfusion imaging.

Methods

We undertook a retrospective analysis of routinely acquired imaging at an academic stroke center serving (for most of the study period) a population of 180 000. Data analysis for this study was approved by the local research ethics committee. All CT perfusion (CTP) scans were reviewed if they were (1) conducted within 6 hours of onset of suspected acute ischemic stroke and (2) had a concurrent NCCT brain. During the period of data acquisition, no specific criteria were defined for CTP request, which was at the discretion of the clinician in charge of the case. Availability was restricted to office hours and presence of a neuroradiologist. Most scans were requested on the basis of clinical uncertainty about the need for treatment with thrombolytic drugs (eg, uncertain time of onset) or uncertainty about clinical diagnosis (eg, prior stroke and established ischemic lesions on CT with possible new deficit).

Noncontrast CT Review

Noncontrast CT scans were blinded and randomly ordered using a computer-generated random numbering process. A random selection of scans was included twice among the sample to assess intrarater agreement. The scans were provided in DICOM format to 5 CT readers (one neuroradiologist [L.W.], 3 experienced stroke neurologists [K.M., T.B., S.C.], and one less experienced stroke physician [M.M.]) with no clinical information, who recorded scan interpretation on a structured sheet. Reviewers were allowed to use DICOM viewer software of their choice and were able to adjust window settings for scans. Most were reviewed with PC-based DICOM

reading software on desktop PCs. Reviewers were asked if scans were normal and which side was involved if abnormal. Each reviewer then independently assessed the presence or absence of swelling, or of hypoattenuation, of each brain region according to the ASPECTS template. Each region could therefore be described as normal, isodense and swollen, hypodense and swollen, or hypodense.

Intrarater agreement was determined using the repeated scans and interrater agreement using all scans.

Regions were categorized as normal, isodense and swollen, or hypodense if the assessments of 2 or more raters (or a majority of raters in the event of one or more being incorrect about lesion side) agreed on the classification.

Perfusion CT

All scans were acquired on a Philips Mx8000 using the following parameters: 0.75-second rotation time, 120-kVp tube voltage, and 200-mAs tube current. A 50-mL bolus of iodinated contrast was injected into an antecubital vein through a large cannula at a rate of 6 mL/sec with a scan delay of 9 seconds. A block of 4×5-mm slices was obtained with a single examination. Processing was conducted on a dedicated CT workstation using MxView 3.51 software that calculates perfusion parameters using the maximum slope method and gives qualitative maps of time to peak (TTP), cerebral blood flow, and CBV. CTP data were reprocessed by one individual (J.B.G.) without knowledge of NCCT findings. Each scan was assessed for the slice most closely corresponding to the brain levels used in the ASPECTS system⁶ and a freehand-drawn region of interest placed within each ASPECTS-defined region (insula, caudate head, lentiform nucleus, internal capsule, and cortical middle cerebral artery territories defined as M1–6) in the affected and contralateral hemispheres (example shown in Figure 1). TTP and CBV values were documented on a minimum of 2 separate times of drawing each region of interest. Values were expressed relative to the contralateral hemisphere as TTP delay (in seconds) and relative CBV as a percentage.

Time to peak delay >3 seconds has been shown to have high sensitivity to ischemia,²³ and relative CBV of 65% to be the optimal threshold for defining infarct core perfusion by CTP where quantitative analysis is unavailable.²⁴ We therefore defined

the tissue compartment of each region of interest as follows: normally perfused tissue, TTP delay <3 seconds; penumbra, TTP \geq 3-second delay and CBV >65%; infarct core TTP \geq 3-second delay and CBV \leq 65%.

Analysis

Intra- and interrater agreement on CT region classification was analyzed using Cohen's kappa statistic with the Fleiss-Cuzick extension for multirater analyses. The sensitivity, specificity, and likelihood ratios (with 95% CIs) for posttest compared with pretest probability of prediction of tissue compartments were calculated.

One-way analysis of variance with post hoc pairwise comparisons using the least significant difference method was used to compare TTP and relative CBV across each of the 3 categories.

Results

Between September 29, 2001, and May 10, 2005, 52 patients (of 983 total admissions) underwent NCCT and CTP examinations in the department. Thirty-two fulfilled study entry criteria and were suitable for analysis. Twenty scans were excluded: 8 that were technically inadequate (6 attributable to

motion artifact, 2 attributable to mistiming of contrast administration), 4 undertaken in nonstroke patients (3 subarachnoid hemorrhages and one arteriovenous malformation), 4 that did not include the middle cerebral artery territory (brainstem or cerebellar imaging), 2 delayed by more than 24 hours after symptom onset, and 2 that could not be retrieved from storage media.

The final diagnosis was ischemic stroke in 29 subjects and nonstroke in 3 (2 functional hemipareses and one epileptic seizure). Because all 3 nonstroke patients were imaged acutely attributable to a clinically suspected stroke event, their studies were included in analysis. The mean age was 65 ± 15 years (range, 26 to 86 years). There were 16 women and 16 men. Median admission National Institutes of Health Stroke Scale score was 11.5 (interquartile range 6 to 17). Median onset to NCCT time was 155 minutes (interquartile range 128.75 to 187.25 minutes), and median time between NCCT and CTP was 10 minutes (interquartile range 6 to 18.5 minutes). Twenty-three of 32 (72%) patients were scanned within 3 hours, and the remaining 9 between 3 and 6 hours. Eighteen subjects (56%) received alteplase treatment.

Only 2 patients had CTP whose field of view included both axial slices needed for ASPECTS. The remainder had CTP whose field of view only included the lower (basal ganglia) slice, therefore 7 of 10 ASPECTS regions. Measurements could not be obtained from 2 regions attributable to established infarction. Consequently, data were available for 228 regions. On NCCT, the categorization was 147 normal regions, 30 isodense and swollen and 51 hypodense regions. On CTP, 150 regions had normal perfusion, 46 were penumbral, and 32 were categorized as infarct core.

Time to peak delay differed significantly by NCCT appearance category, increasing from normal to isodense swollen to hypodense brain regions ($P < 0.001$, Figure 2A).

Cerebral blood volume (expressed as relative CBV %) was significantly higher in regions categorized as isodense and swollen compared with either normal or hypodense regions (overall $P = 0.040$, Figure 2B; post hoc analyses $P = 0.016$ for normal-appearing versus isodense swelling, $P = 0.023$ for isodense swelling versus hypodense).

There was a significant difference in the proportion of regions with normally perfused tissue, penumbra, and core according to the NCCT appearance (χ^2 test for trend $P < 0.0001$, Figure 3) with a higher probability of infarct core perfusion pattern in hypodense tissue and higher probability of penumbral pattern in regions that were swollen.

Sensitivities, specificities, and positive predictive values with likelihood ratios (and 95% CIs) for the positive test result, for NCCT appearance, and tissue compartments are shown (Table). Isodense swelling had low sensitivity but good specificity for penumbral perfusion. The appearance of isodense swelling was associated with reduced likelihood of core perfusion. Hypodensity had low sensitivity but high specificity for core perfusion.

Overall intrarater agreement on hypodensity was good (kappa=0.659) and for swelling was moderate (kappa=0.515). For individual raters, kappa ranged from 0.309 to 0.827 for hypodensity and from 0.224 to 0.634 for swelling.

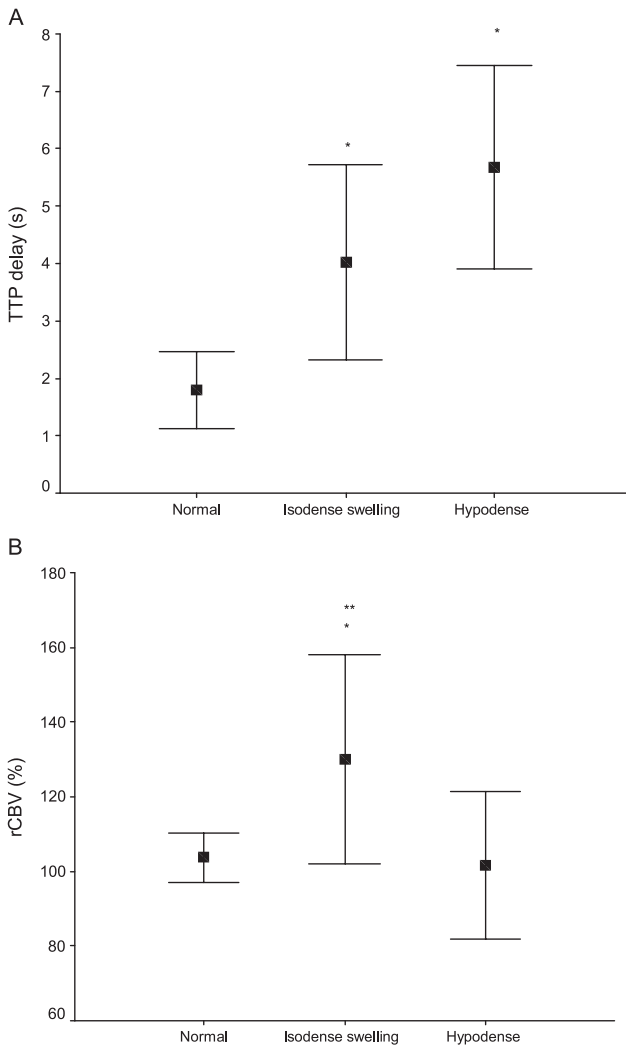


Figure 2. A, TTP delay and (B) CBV relative to the normal hemisphere according to brain region appearance. Figures are means; error bars represent SEs of the means. * $P < 0.05$ compared with normal regions; ** $P < 0.05$ compared with hypodense regions.

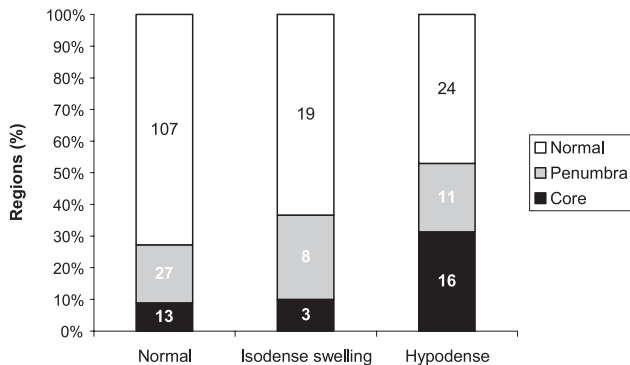


Figure 3. Proportion of regions having perfusion characteristics of core, penumbra, and normal tissue. The absolute numbers of regions in each category are specified in the graph.

However, interrater agreement was poor for both hypodensity ($\kappa=0.158$) and isodense swelling ($\kappa=0.088$). An example of a CT on which there was agreement on presence of isodense swelling is shown together with associated CTP maps (Figure 4).

Discussion

Physiological imaging with MRI or CT (perfusion-diffusion mismatch or CTP) to define the presence of an ischemic penumbra allows clinicians to make acute treatment decisions based on individual pathophysiology. Although technological advances have presented clinicians with these data before prospective, randomized trials can adequately test the hypotheses that they generate, observational evidence suggests that such physiological findings are relevant to the safety of, and time window for, thrombolysis.^{25–28} However, because such imaging is not routinely available in most centers worldwide, most decisions on thrombolytic treatment continue to be informed only by NCCT.

Anatomically extensive EIC on NCCT signifies poor outcome and higher bleeding risk in thrombolytic trials and prospective studies.^{5,6} Improved recognition of EIC over time is evident from reanalysis of CT scans from thrombolysis trials, all reporting a higher prevalence of EIC on detailed, usually structured, review than in the original study groups' estimation, eg, from 31% to 52% in the National Institute of Neurological Disorders and Stroke, 75% to 89% in PROACT 2, and 47% to 66% in ECASS 2.^{3–5,29,30} The significance of EIC in acute thrombolytic treatment decisions within 3 hours remains the subject of debate,^{31,32} and there is no definitive

evidence that intravenous alteplase is ineffective or harmful even where EIC is extensive.⁴ Interpretation of these trial findings is confounded by changes in CT technology and observer expertise over time, different trial time windows, and subjective definition of hypodensity. Some apparently contradictory findings such as instances of sometimes dramatic recovery from apparently extensive EIC³ may result from failure to distinguish swelling from hypodensity.

Our CTP findings support previous observations derived from combining NCCT and MR perfusion^{7,22} and confirm that, within the first 6 hours after stroke onset, swelling and hypodensity on NCCT differ in their perfusion characteristics and therefore their underlying pathophysiology. Isodense swelling corresponded with increased CBV and with perfusion parameters of the ischemic penumbra, whereas hypodensity corresponded with more severe ischemia and with infarct core perfusion. NCCT may therefore yield evidence of tissue viability.

There are important limitations in our study. The generalizability of these findings is unknown; our sample included predominantly a population with moderately severe stroke syndromes approximately 2 to 4 hours after onset. However, because this was a retrospective study, the population who underwent CTP was scanned at clinical request and therefore almost certainly represented a selected group who had a higher probability of NCCT scans that were difficult to interpret. In addition, there were some patients in whom the final diagnosis was not stroke. These factors contribute to the limited sensitivity and poor interobserver agreement that we found and may also partly explain the unexpected finding that in hypodense regions, mean CBV was normal rather than reduced, as would be expected. Although specificity was high for prediction of tissue compartments, the sensitivity of either feature was poor, particularly for isodense swelling. Hypodensity in particular increased the likelihood of an infarct core perfusion pattern more than 3-fold, whereas isodense swelling reduced the likelihood of core perfusion. The moderate to excellent intraobserver agreement for both swelling and hypodensity indicates that consistent interpretation is possible, but the poor interrater agreement means that prior consensus on CT definitions and training is certainly required before these separate features could be more widely used. Although better interobserver agreement is reported,² agreement between raters on the presence of NCCT EICs may be limited in the absence of clinical information and our kappa

Sensitivity, Specificity, and Likelihood Ratios With 95% CIs for Prediction of Tissue Compartment From NCCT Appearance*

	Sensitivity	Specificity	Overall Agreement	Likelihood Ratio (95% CI)
Prediction of penumbra				
Isodense swelling	17.4%	87.9%	73.7% (168/228)	1.44 (0.68–2.90)
Hypodensity	23.9%	78.0%	67.1% (153/228)	1.09 (0.60–1.88)
Prediction of core				
Isodense swelling	9.4%	86.2%	75.4% (172/228)	0.68 (0.22–1.88)
Hypodensity	31.4%	91.0%	77.6% (177/228)	3.47 (1.87–6.34)

*Likelihood ratio expresses the ratio of posttest to pretest likelihood.

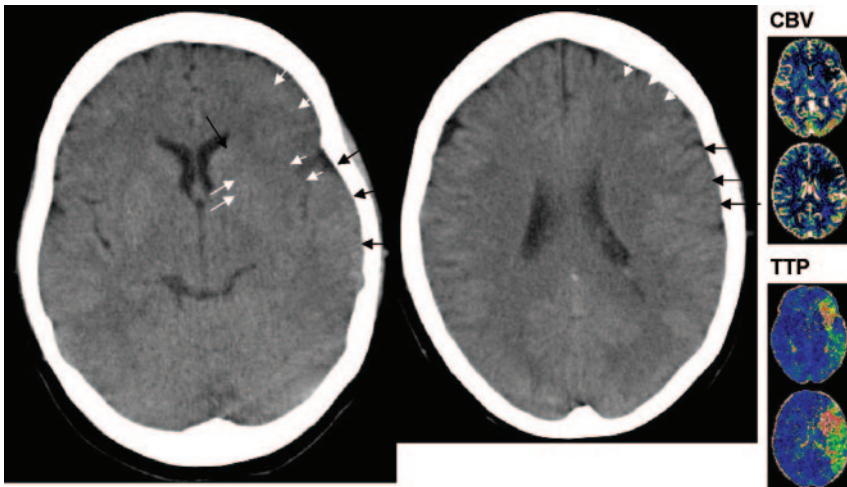


Figure 4. Example CT scan (ASPECTS levels: C:40; W:80) coded as having regions of isodense swelling with associated TTP and CBV maps. Left middle cerebral artery occlusion with isodense swelling in caudate, M2, M5, and hypodensity of lentiform nucleus, insula, M1, M4. Black arrows indicate regions of isodense swelling. White arrows indicate regions of hypodensity.

values signifying poor interrater agreement are in line with those reported previously, for example, in the ASPECTS study in which neurologists blind to lateralization achieved a kappa of 0.34 for lateralization of CT abnormalities compared with 0.353 in our study. Knowledge of side and neurological features improves agreement, and in addition, the varied professional background of observers, and case selection issues noted here, will exaggerate disagreements. The use of small tissue volumes for perfusion measurement increases the variability and reduces the precision of our findings.

Confirmation in a larger sample is certainly required; only one third of regions were categorized as isodense and swollen or hypodense. The time course and clinical (and tissue) implications of isodense swelling on NCCT require definition and are the subject of further study. Because we did not routinely have follow-up NCCT, we relied on perfusion parameters reported by other groups to be predictive of infarct core and penumbra; although we believe the thresholds we used are robust, correlation of these NCCT findings with tissue outcome is important. If isodense swelling signifies penumbra, then this appearance should be associated with significant tissue recovery in those who reperfuse early.

Despite limitations, our findings support the hypothesis that appearances on NCCT reflect tissue perfusion status. The poor sensitivity and interobserver agreement of isodense swelling are likely to limit clinical use.

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Disclosures

None.

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