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# Evaluation of Early Computed Tomographic Findings in Acute Ischemic Stroke

Michael P. Marks, MD; Eric B. Holmgren, PhD; Allan J. Fox, MD; Suresh Patel, MD; Rudiger von Kummer, MD; Juergen Froehlich, MD

**Background and Purpose**—Detection of large, hypoattenuated brain-tissue volume on hyperacute CT scan has been suggested as an exclusion criterion for early intravenous tissue plasminogen activator (IV-tPA) treatment. This study assessed the reliability of detection for these findings and their relationship to outcome.

**Methods**—Fifty hyperacute CT scans (<6 hours after ictus) were selected from a randomized trial evaluating IV-tPA (ATLANTIS trial). Three neuroradiologists blinded to all clinical information evaluated scans for degree of MCA territory involvement (<33% or >33%) and the presence of a hyperdense MCA. Evaluations were compared with 24-hour scan results, 30-day infarct volumes, and baseline NIH stroke scale scores (NIHSS).

**Results**—Readers reliably evaluated the degree of MCA territory hypodensity (intraclass correlation=0.53,  $P<0.001$ ), with all 3 readers agreeing in 36 of 50 cases (72%). They correctly called >33% involvement with a sensitivity of 60% to 85% and a specificity of 86% to 97%. The baseline NIHSS was higher when >33% MCA hypodensity was seen ( $P=0.021$ ). Detection of significant hypodensity (>33%) correlated with poorer outcome. When >33% hypodensity was not detected, mean 30-day infarct volumes were 27.0 to 33.0 cm<sup>3</sup>, versus 84.3 to 123.1 cm<sup>3</sup> when >33% hypodensity was present ( $P=0.002$ ).

**Conclusions**—Detection of MCA territory hypodensity on hyperacute CT scans is a sensitive, prognostic, and reliable indicator of the amount of MCA territory undergoing infarction. (*Stroke*. 1999;30:389-392.)

**Key Words:** cerebral infarction ■ cerebral ischemia ■ tomography, x-ray computed

Computed tomographic scanning previously had been used in the setting of presumed acute ischemic stroke to exclude hemorrhage stroke and other possible causes for a presenting patient's symptoms. It was not considered an imaging tool capable of yielding early prognostic information in ischemic stroke. More recently, with the administration of intravenous tissue plasminogen activator (IV-tPA) in the first hours of stroke, CT scanning has demonstrated a possible role as a prognostic and triage test.<sup>1-3</sup> The observation of early infarct signs involving extensive areas of the middle cerebral artery territory has been implicated in poor outcome.<sup>2,3</sup> Treatment with IV-tPA had no beneficial affect in this group and increased the likelihood of fatal intracranial hemorrhage.<sup>3</sup> However, exclusion of this group with more subtle early signs of infarct has proven difficult in 1 large multicenter trial.<sup>2</sup> This study was designed to assess the interrater reliability of these early CT findings among blinded neuroradiologists after ischemic stroke. It also evaluated the association of these early observations with short-term (24-hour) and long-term (30-day) findings.

## Subjects and Methods

Fifty hyperacute scans (<6 hours after ictus) were selected from a randomized multicenter trial evaluating IV-tPA in early stroke (ATLANTIS trial, Genentech Inc). Patients participating in this study were randomized to IV-tPA or placebo. No anticoagulant or antiplatelet therapy was given in the first 24 hours under the study protocol. Scans were chosen to give a representative mix of CT findings, including early evidence of middle cerebral artery territory involvement and the presence of a hyperdense middle cerebral artery sign (HMCAS). Scans were not limited to patients with middle cerebral artery (MCA) territory events. These baseline scans were selected by 1 neuroradiologist (M.P.M.) with the benefit of follow-up scans at 24 hours and 30 days. Three neuroradiologists (A.J.F., R.V.K., S.P.) were then asked to evaluate baseline scans blinded to all clinical information. No randomization data (drug versus placebo) were made available or evaluated as part of this study. Readers were given only the baseline scans to evaluate and no clinical data. Each scan was assessed for pathological parenchymal hypoattenuation and sulcal effacement. The degree of involvement of the middle cerebral artery territory was also estimated as either <33% or >33%. When no hypodensity was present or if another territory besides the MCA was involved, these patients were included in the group having <33% MCA territory involvement for purposes of statistical evaluation. In addition, scans were separately

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From Stanford University, Stanford, Calif (M.P.M.); Genentech, South San Francisco, Calif (E.B.H., J.F.); University of Western Ontario, London, Ontario, Canada (A.J.F.); Henry Ford Hospital, Detroit, Mich (S.P.); and the University of Dresden (R.von K.), Dresden, Germany.

Two of the authors have been directly employed by Genentech, and the first author, Michael P. Marks, has acted as a consultant to Genentech. However, this article is not directly based on clinical results obtained by treating patients with tPA or other products manufactured by Genentech.

Correspondence and reprint requests to Michael P. Marks, MD, Director of Neuroradiology, Stanford Stroke Center, Stanford University Medical Center, 300 Pasteur Dr, Stanford, CA 94305-5105. E-mail: m.marks@stanford.edu

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**TABLE 1. Postinfarct Hypodensity at 24 Hours**

Region	No.
MCA (<1/3)	24
MCA (>1/3)	15
PCA/VB	3
ACA	1
No hypodensity	7

adjudged for an HMCAS using a previously described definition which indicated that the middle cerebral artery should be more dense than its counterpart and denser than any visualized artery or vein.<sup>4,5</sup>

The blinded baseline scan evaluations were compared with 24-hour and 30-day scan results. The 24-hour scans were evaluated for the vascular territories involved (MCA, anterior cerebral artery, posterior cerebral artery, or vertebrobasilar artery). If the MCA territory was involved, this was evaluated as showing <33% or >33% hypodensity at 24 hours. These 24-hour scan results were used as a "gold standard" to evaluate sensitivity and specificity for the observation of hypoattenuation on the baseline scans.

Baseline scan evaluations for hypodensity in the MCA territory and an HMCAS sign were also compared with the volume of the infarct as determined on the 30-day scan. To determine infarct volume the region of hypodensity was outlined on the individual slices of the 30-day scan. Individual regions of interest were then measured for area using a digitizing tablet (Sigma Scan, Jandel Scientific). These regions were corrected for CT slice thickness and summed to determine a volume of tissue infarcted. In addition baseline scan readings were correlated with clinical presentation using the NIH stroke scale (NIHSS) at the time of baseline scanning. The 30-day stroke volumes were done on 44 subjects. Four patients died before 30 days of follow-up, and 2 patients did not have scans at 30 days. NIHSS was available for all 50 subjects.

The interrater reliability of the evaluations of the baseline scans was assessed using the intraclass correlation coefficient.  $\kappa$  coefficients were calculated as well for each pair of raters.<sup>6</sup> Comparisons of infarct volume and NIHSS between those subjects with <33% and >33% hypodensity in the MCA territory were made using a 2-sample *t* test. The overall assessment of the relationship between the raters' evaluations and the stroke volume as well as the NIHSS was made using generalized estimating equations.<sup>7</sup> In this model the rater's evaluations were treated as dependent binary variables and the stroke volume as well as the NIHSS were treated separately, as explanatory variables. The probability value reported from the generalized estimating equations model assesses the significance of the regression coefficients for stroke volume and for the NIHSS.

## Results

Table 1 shows the 24-hour scan findings, which were evaluated for hypodensity and served as a gold standard for the degree of MCA territory involvement. There was no involvement of the MCA territory in 11 of 50 cases (22%), a <33% MCA hypodensity in 24 of 50 cases (48%), and >33% involvement in 15 of 50 cases (30%).

Table 2 compares the baseline MCA hypodensity readings with the 24-hour MCA hypodensity scan results. The sensitivity of the baseline scan readings for the detection of >33% MCA territory hypodensity was 60%, 67%, and 87% for the 3 readers while the specificities were 86%, 92%, and 97%. The table groups rater evaluations of baseline scans based on the 2 possible 24-hour scan results (<33% or >33% MCA hypodensity). There was a statistically significant difference in the proportion of patients identified with <33% involvement on the baseline scans when patients were grouped based on the 2 outcomes at 24 hours. For example, reader 1

**TABLE 2. Evaluations of MCA Hypodensity vs 24-Hour CT Scan Results**

Rater No.	Rater Evaluation	24-Hour Scan Results, n (%)		<i>P</i>
		<33%	>33%	
1	<33%	32 (92)	5 (33)	0.0001
	>33%	3 (8)	10 (67)	
2	<33%	34 (97)	2 (13)	0.0000
	>33%	1 (39)	13 (87)	
3	<33%	30 (86)	6 (40)	0.0019
	>33%	5 (14)	9 (60)	

correctly identified 92% (32 of 35 cases) in the group as having <33% MCA territory involvement at 24 hours. On the other hand, reader 1 incorrectly identified <33% MCA hypodensity in only 5 of 15 cases (33%) in the group with >33% involvement at 24 hours. The statistically significant difference in these proportions indicates that the readings are not based on random choice or guessing for any of the 3 readers.

Table 3 shows the extent of agreement among the 3 readers in assessing whether >33% hypodensity existed in the MCA territory and in evaluating for HMCAS. Overall, the 3 readers completely agreed about MCA hypodensity in 36 of 50 cases (72%). In 28 of 50 subjects (56%) none of the readers found >33% involvement in the MCA territory, and in 8 of 50 subjects (16%) all 3 readers found >33% MCA territory involvement. At least 1 reader found >33% MCA involvement in 22 of 50 subjects (44%), and in 11 of 50 subjects (22%) at least 2 readers found >33% MCA involvement. As shown in Table 4, this level of agreement for MCA hypodensity corresponds to an intraclass correlation of 0.53 ( $P<0.0001$ ), indicating that the amount of agreement seen is more than what would be expected from chance alone. The pairwise  $\kappa$  coefficients were 0.65, 0.44, and 0.50, each of which is significantly different from zero.

Strong agreement did not exist among the 3 readers in their evaluations of HMCAS. As shown in Table 3, 13 of 50 subjects (26%) were counted as having an HMCAS by none of the readers, 34 of 50 subjects (68%) by at least 1 of the

**TABLE 3. Agreement Among Readers in the Evaluation of >33% MCA Territory Hypodensity and HMCAS**

	No. Observed/No. of Cases (%)
Hypodensity in >33% of the MCA Territory	
0	28/50 (56)
≥1	22/50 (44)
≥2	11/50 (22)
3	8/50 (16)
HMCAS	
0	13/50 (26)
≥1	34/50 (68)
≥2	18/50 (36)
3	11/50 (22)

**TABLE 4. Intraclass Correlation Coefficients and  $\kappa$  Values**

	Hypodensity		HMCAS	
	$\kappa$	95% CI	$\kappa$	95% CI
1 vs 2	0.65	0.41–0.89	0.33	0.07–0.58
1 vs 3	0.44	0.16–0.72	0.20	–0.04–0.44
2 vs 3	0.50	0.24–0.77	0.63	0.40–0.86

Values are based on pairwise agreement. Overall agreement for hypodensity was 0.53 ( $P < 0.001$ ); for HMCAS, 0.36 ( $P < 0.0001$ ).

readers, 18 of 50 subjects (36%) by at least 2 of the readers, and 11 of 50 subjects (22%) by all 3 readers. Overall, the readers agreed in 48% of the subjects, which is a lower rate than for the presence of tissue hypodensity in the MCA territory. The intraclass correlation coefficient (Table 4) corresponding to this level of agreement is 0.36 ( $P < 0.001$ ), indicating a statistically significant degree of agreement among the readers. No significant relationship could be found between the HMCAS and infarct volume at 30 days or baseline NIHSS.

The correlation of the MCA territory readings for all 3 readers taken together with the final 30-day infarct volume was found to be statistically significant ( $P = 0.0002$ ), with a greater final infarct volume associated with a greater probability of declaring >33% MCA territory hypodensity involvement. This correlation is illustrated in Table 5 for each individual reader.

The correlation of the MCA territory readings of all 3 readers taken together was also found to be associated with the NIHSS at baseline ( $P = 0.021$ ), with a greater NIHSS associated with a greater probability of declaring >33% MCA territory involvement. The associations are illustrated in Table 6.

**Discussion**

The reliability of early CT findings in the detection of acute ischemic stroke as well as the reproducibility of scan reading has been a matter of some controversy in screening for acute stroke. The results of the European Cooperative Acute Stroke Study (ECASS) trial suggested that when a careful retrospective analysis of early CT findings could be performed and patients were excluded from treatment with >33% of the MCA territory showing hypodensity, early IV-tPA was beneficial compared with placebo.<sup>2</sup> This study was encumbered by a large number of protocol violations, most often related to inclusion of patients that were retrospectively found to have early CT findings of stroke. The ECASS investigators recognized that the identification of that subgroup of patients with early CT findings may indeed prove to be difficult.<sup>2</sup>

**TABLE 5. Comparison of Baseline CT MCA Territory Hypodensity to 30-day Infarct Volume**

Reader No.	<33%, cm <sup>3</sup> *	>33%, cm <sup>3</sup> *	<i>P</i>
1	27±5.75	112.3±27.2	0.0004
2	24±5.06	123.1±24.9	0.0001
3	33±10.2	84.3±15.9	0.010

\*Final (30-day) infarct volume, mean±SE.

**TABLE 6. Comparison of Baseline CT MCA Territory Hypodensity to Baseline NIHSS**

Reader No.	<33%*	>33%*	<i>P</i>
1	11.6±0.99*	14.8±1.76	0.12
2	11.1±1	15.8±1.5	0.012
3	11.3±0.99	15.4±1.64	0.037

\*NIHSS, mean±SE.

Further analysis of the ECASS data (performed in a retrospective fashion) has indicated that in patients with evidence of hypodensity involving <33% of the MCA territory early IV-tPA has a therapeutic benefit.<sup>3</sup> Moreover, when hypodensity involves >33% of the MCA territory, IV-tPA does not confer benefit and the risk of hemorrhage increases, complicating the IV-tPA therapy.

A few studies have attempted to look at the reliability of early CT and the interobserver agreement for the detection of hypodensity and have shown mixed results.<sup>3,8–10</sup> von Kummer et al<sup>8,9</sup> in 2 separate publications have suggested that neuroradiologists are capable of detecting hypodensity in the MCA territory with good interobserver agreement. However, complete pairwise agreement between readers was low in a study that evaluated the ability of readers to categorize the percent of MCA territory involved.<sup>8</sup> The authors did suggest that this may be due to the fact that readers were asked to judge 20% increments of territorial involvement rather than a simpler formula, such as >33% or <33% of the MCA territory. In a more recent article (also using ECASS study patients) evaluations for >33% or <33% involvement of the MCA territory, von Kummer et al<sup>3</sup> found a low  $\kappa$  value ( $\kappa = 0.36$ ), despite a high interobserver agreement (86%). This apparent paradox can be partly explained by the fact that a low  $\kappa$  can be seen with a low prevalence of patients with significant hypodensity in the MCA.<sup>3</sup> Most of those patients with significant MCA hypodensity were excluded from the ECASS study before treatment. In addition the fact that 20% of the scans evaluated were rated as being of poor quality despite being readable was implicated in the low  $\kappa$  observed. A recently published study by Schriger et al<sup>10</sup> evaluated the ability of nonneuroradiologists to primarily detect intracranial hemorrhage in acute stroke scans; however, the ability to evaluate acute infarction on the basis of hypodensity was also rated. Scans in this study were divided on the basis of consensus processing into easy, intermediate, or difficult to detect acute infarctions. The percentage of physicians correctly determining acute infarction varied greatly across subspecialties and with the type of infarction present.

This study differs from previous studies in that scans were preselected to be of good quality and to provide a significant percentage of scans, with the finding of >33% hypodensity in the MCA territory. The data suggest good to excellent interobserver reliability in the detection of >33% or <33% hypodensity of the MCA territory for neuroradiologists evaluating acute-phase scans without clinical information when evaluating the baseline CT scan.<sup>11</sup> In addition this study used the short-interval (24-hour) scan as a gold standard for the detection of significant hypodensity. This has allowed

for a measure of accuracy in the ability of the early CT scan to discriminate  $>33\%$  or  $<33\%$  hypoattenuation in the MCA territory. Assuming the 24-hour scan is the gold standard, a high degree of sensitivity and specificity exists for the evaluation of  $>33\%$  hypodensity in the MCA territory. The early hypoattenuation that is visualized may represent cytotoxic edema.<sup>12,13</sup> It has been argued that brain edema such as this does not resolve with reperfusion and that these changes are most likely permanent.<sup>13</sup> Therefore, the use of the 24-hour scan is unlikely to underestimate those cases in which extensive hypoattenuation is present on the initial scan. However, 1 source of possible error is that reperfusion can cause more extensive edema to be present.<sup>14</sup> Therefore, it is always possible that the number of cases with  $>33\%$  hypoattenuation, based on the 24-hour scan, represents an overestimate of the scans that would have shown involvement at baseline. Nevertheless, data presented here also show a significant correlation with  $>33\%$  MCA territory involvement and the final infarct volume (at 30 days). All 3 of the readers identified a subset of patients with significantly larger final infarcts based on the initial scan.

The HMCAS has also been evaluated for its prognostic ability in the setting of thrombolytic treatment.<sup>15</sup> When the HMCAS has been coupled with a high NIHSS score ( $\geq 10$ ), patients were less likely to be clinically improved and had larger infarcts than those who had similar NIHSS scores but no evidence of an HMCAS.<sup>15</sup> However, the authors in this study found that the presence of an early major neurological deficit was a better predictor of poor outcome than a positive HMCAS. von Kummer et al<sup>8</sup> have reported that there is moderate to substantial interobserver agreement for the detection of HMCAS even when the observers are clinically blinded. While this study did find a statistically significant degree of agreement among the readers for HMCAS, the degree of agreement was not as strong for HMCAS as it was for  $>33\%$  or  $<33\%$  MCA territory hypodensity. This study did not use a gold standard such as angiography to confirm the presence of MCA thrombosis, making sensitivity and specificity data unavailable.

In conclusion this study has shown that well-trained blinded observers are capable of assessing the degree of MCA hypodensity for  $>33\%$  or  $<33\%$  involvement with a good deal of interobserver reliability. In addition when these results are measured against a gold standard there is a high specificity for these readings. The sensitivities obtained for  $>33\%$  MCA involvement (60% to 87%) indicate that there is room to improve detection of  $>33\%$  MCA hypodensity. This study underscores the need to have well-trained physicians evaluating scans and to have high-quality scans for these interpretations. Tools capable of showing higher contrast between ischemic and nonischemic tissue, such as diffusion-weighted MR imagers,<sup>15-18</sup> may replace these techniques. However, with the widespread availability of CT scanning, studies such as this suggest that CT can be applied as a

screening tool in the setting of acute ischemic stroke. In addition, coupling the noncontrast CT scan to another CT technique, xenon-CT cerebral blood flow, recently has been shown to improve sensitivity in the detection of acute stroke<sup>19</sup> and may benefit the prognostic reliability of CT scanning.

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