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AJNR Am J Neuroradiol 1993, 14 (1) 3-13
http://www.ajnr.org/content/14/1/3

Neuroradiologic Evaluation of Patients with Acute Stroke Treated with Recombinant Tissue Plasminogen Activator

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PURPOSE: 1)To describe the effectiveness and safety of thrombolytic therapy in patients with acute atherothrombotic and embolic stroke and 2) to study the variables of the occlusion site as seen on the angiograms, the CT signs of early ischemia, the hyperdense middle cerebral artery sign (HMCAS), and the size of the infarcts as seen on the 24-hour CT scan. **METHODS:** Ninety-three of 139 patients with acute stroke were treated with intravenous tissue plasminogen activator (rt-PA). The initial disease and the effects of treatment were assessed with both CT and cerebral angiography. **RESULTS:** Recanalization of occluded arteries occurred in 32 patients and was more frequent in distal occlusions. In general, patients displaying recanalization tended to develop small infarcts and patients with a HMCAS tended to develop large infarcts. Patients with signs of early ischemia developed large infarcts. The presence of a HMCAS was 100% fic for an occluded artery, but only 27% sensitive. Hemorrhagic transformations occurred in the distribution of the occluded arteries in 32 patients. **CONCLUSIONS:** Emergency cerebral angiography, which can be carried out relatively safely, adds important information about the nature and extent of the arterial occlusions, and the recanalization efficacy of fibrinolytic therapy for patients with acute stroke. Fibrinolytic therapy can be carried out with a relatively low complication rate that still needs to be correlated with the clinical benefits of the treatment. Fibrinolytic therapy in the doses utilized in this study, is more effective with distal than with proximal carotid territory occlusions.

Index terms: Thrombolysis; Brain, infarction; Cerebral angiography, indications

AJNR 14:3–13, Jan/Feb 1993

The treatment of patients with acute stroke due to atherothrombotic and embolic cerebrovascular disease is predicated on obtaining lysis of the thrombus before irreversible ischemic changes occur in the brain. A multicenter dose escalation study to evaluate the efficacy and safety of intravenous two-chain recombinant tissue plasminogen activator (rt-PA; duteplase) in patients presenting with an acute thrombotic or embolic stroke has been carried out. The selection criteria, study protocol, dose-rate guidelines, intracranial hemorrhagic events observed, and the overall recanalization efficacy has been reported recently (1).

This paper describes the sites of angiographic occlusions on entry into the study, the effects of treatment on recanalization and hemorrhagic transformation, and the relationship of the entry CT scans and entry arteriograms to the likelihood of hemorrhagic transformation and recanalization. The significance of the size of the infarcts at 24 hours after stroke, the complications of angiography in the presence of an acute stroke, and the limitations of the study are also considered.

Materials and Methods

Between June 1987 and May 1990, 139 patients (21 to 80 years of age) from 16 major institutional centers in

Received March 26, 1992; accepted September 22.

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AJNR 14:3–13, Jan/Feb 1993 0195-6108/93/1401–0003

North American and the Federal Republic of Germany were initially screened for the onset of acute stroke secondary to carotid or vertebrobasilar large artery occlusion (Table 1). Strict clinical inclusion and exclusion criteria were imposed for study entry (1). All patients were required to have symptoms of acute focal cerebral or brain stem ischemia occurring no later than 8 hours from the expected time of rt-PA therapy. Based upon immediate angiography, 27 of the 139 patients were excluded because of the absence of detectable occlusions, or stenosis without occlusion. Of the remaining 112 patients, eight were excluded because of arterial dissections (n = 6), or incidental aneurysms (n = 2). Thus 104 patients received rt-PA and were available for a safety analysis that has been reported elsewhere (1). Eleven patients were further excluded from the analysis because of incomplete drug infusions, possible allergic reactions, or extracerebral angiographic complications, leaving 93 patients available for a recanalization efficacy analysis. Each patient received a sing doe of rt-PA at one of nine dose-rate tiers. The dose-rates escalated from 0.12 MIU/kg·60 minutes to 0.75 MIU/kg·60 minutes. Unfortunately, before the optimum dose-rate was ascertained the study was prematurely terminated through the withdrawal of this rt-PA from clinical trials following a patent suit.

Computed Tomographic Criteria

All patients underwent noncontrast computed tomography (CT) scanning on admission to determine eligibility for the trial. The scans were obtained using a variety of scanners, with scan thicknesses varying between 5 and 10 mm. CT scan exclusion criteria included high-density lesions consistent with hemorrhage, evidence of significant mass effect or a large midline shift, evidence of a lacunar infarct that may have been responsible for the admitting symptoms, or other lesions such as intracranial tumor, arteriovenous malformation, or aneurysm. Noncontrast CT scans were also obtained at 24 hours and between 10 and 14 days after rt-PA administration, as well as at any time within the study interval when clinical deterioration occurred.

At the Core Neuroradiology Center, the scans were examined for signs of early ischemia and for the presence of a hyperdense middle cerebral artery sign (HMCAS). The volumes of the infarcts on the 24-hour scans were also assessed. The neuroradiologist was not blinded to the side of clinical or angiographic involvement.

Signs of early ischemia were defined as sulcal effacement with loss of the gray-white differentiation with no mass effect (2). The presence of a HMCAS, defined as a middle cerebral artery (MCA) denser than its contralateral counterpart, and presumed due to an embolic occlusion within the MCA stem (3), was also documented. Bland infarcts, as well as hemorrhagic transformations (HTs) consisting of hemorrhagic infarctions (HI) (Fig. 1) or parenchymatous hematomas (PH) (Fig. 2) were documented on the 24-hour and other scans. The operational definitions

TABLE 1: Patient selection: 139 patients with focal cerebral or brain stem ischemia and angiography

27	Normal or stenotic arterial disease
6	Carotid dissections
2	Occlusions with aneurysms
11	Miscellaneous (incorrect drug formulation possible allergy to drug, extracerebral angiographic complications, etc)
46	Total patients excluded
93	Patients entered study

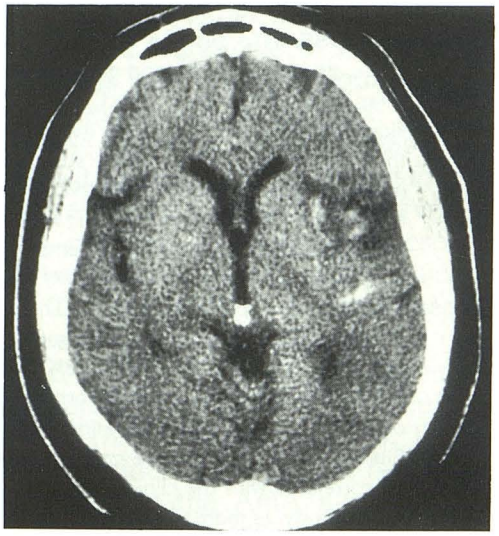


Fig. 1. A hemorrhagic infarction consisting of an area of low density with peripheral areas of high density is seen in the distribution of the left middle cerebral artery.

of HI and PH were developed during the course of the study and are described in Appendix A.

Infarction size was measured on the 24-hour CT scans in 84 of the 93 patients. Infarction size was not assessed in nine patients with the PHs because it was impossible to separate the low-density edematous collar surrounding the hemorrhage from low density due to the infarction. However, two patients with PHs were included for size measurements since the hematomas were in areas remote from the infarcts (the opposite occipital lobe and the cerebellum). The infarction volume was calculated as the sum of the areas of low density from the individual scan sections emcompassing the low-attenuation lesions. A video-imaging program was used for the determinations (Sigma-Scan Measurement Program; Jandel Scientific, Corte Madera, CA). The 24-hour scans rather than later scans were chosen for this assessment to eliminate the contribution of the "fogging" effect.

Because of the heterogeneity of the arterial occlusions in the 84 patients, the infarction volumes were assessed in two groups: analysis A, the group of 84 patients, and analysis B, a relatively homogeneous subset of 71 patients with infarctions limited to occlusions in the MCA territory, and in whom infarct sizes could be determined. In this latter group, only patients with opacification of the MCA territory

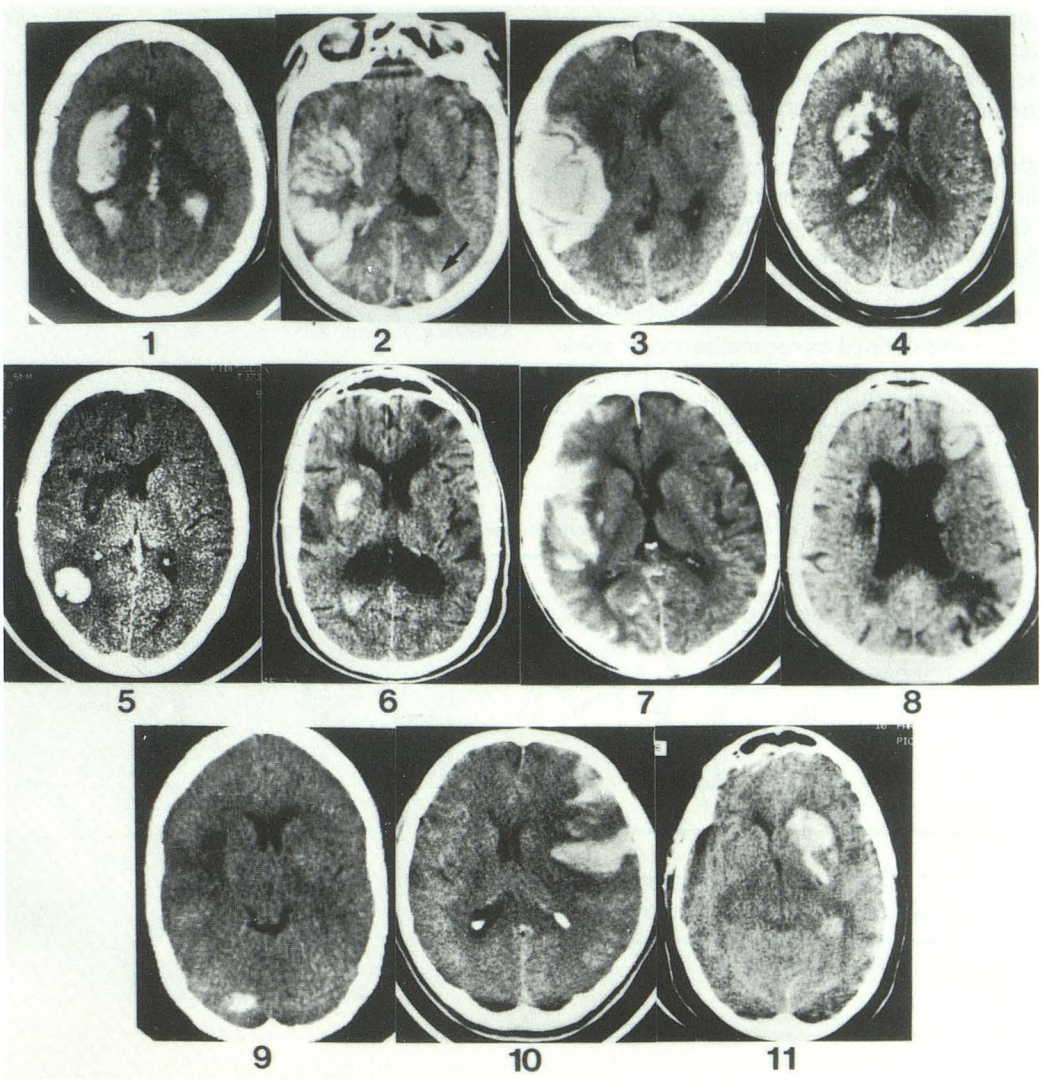


Fig. 2. Composite illustration of 11 patients with prenchymatous hematomas. Note that in case *2* a hematoma (*arrow*) occurred in the occipital lobe on the opposite side from the hemorrhagic infarct. In case *9*, a hematoma occurred in the cerebellum, although the infarct involved the temporal lobe and adjacent opercula. Also note that cases *2* and *10* could be classified as either hemorrhagic infarcts or parenchymatous hematomas.

were included (patients with occluded extracranial carotid arteries without visualization of the ipsilateral MCA in whom contralateral carotid artery injections angiograms were not carried out were excluded).

Angiographic Criteria

Cut film as well as digital subtraction angiography were performed depending on availability at the different centers. Ionic contrast agents were used in most of the studies. The volume of contrast agents used and the rates of injection were at the discretion of the different angiographers.

Angiographic inclusion criteria consisted of unequivocal complete occlusion of the extracranial carotid artery or intracranial carotid artery or its branches, or occlusion in the vertebrobasilar system. Exclusion criteria consisted of arterial stenosis with or without a luminal defect as the sole lesion, suspected dissection of the carotid or vertebrobasilar arteries, coexistent aneurysm, arteriovenous malformation, or nonatherosclerotic arteriopathy (eg, vasculitis).

Following demonstration of the occlusion, each patient received a single preassigned dose of intravenous rt-PA for 60 minutes, at a constant infusion rate. Repeat angiography was carried out immediately following completion of the infusion. Heparin use was confined to that necessary to maintain catheter patency during angiography and in no instance exceeded 2000 IU total per patient at any institution. Heparin was also forbidden for 24 hours following the rt-PA infusion and oral anticoagulants were not allowed within 72 hours of the treatment.

The angiograms and CT scans were interpreted at each center and then adjudicated at the Core Neuroradiology Facility. Comparisons between the pre- and post-rt-PA infusion angiograms were made in an unblinded manner to

determine the arterial perfusion grade at each dose-rate. When differences in interpretation occurred, the core neuroradiologist and one of his coauthors adjudicated the final decision. Systematic intra- and interobserver analyses were not carried out.

The distribution of angiographic occlusions is displayed in Table 2. The extent of angiographic perfusion after treatment was classified according to TIMI grades (4) and classified by degree of recanalization after grading as described in Appendix B (Fig. 3). Complete recanalization was defined as normal opacification of all occluded arteries. Partial recanalization was defined as recanalization of some but not all the occluded arteries (Fig. 3). In many patients, the circle of Willis and the presence of collateral channels were not demonstrated because four-vessel angiography was not routinely carried out. In 12 of the 23 patients with extracranial carotid artery occlusions, the opposite carotid artery was injected allowing an assessment of the ipsilateral intracranial vascular anatomy to be made. In 11 of the 23 patients, only the ipsilateral carotid artery was opacified.

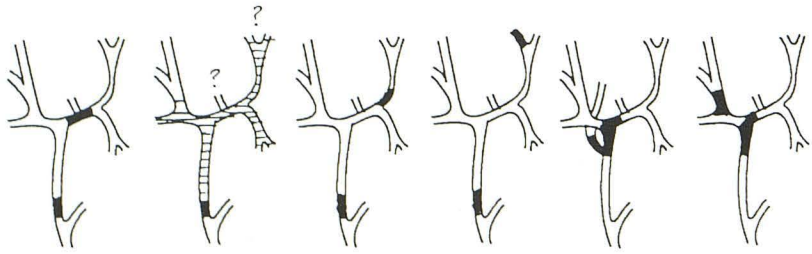
Recanalization and Clinical Outcome

Clinical outcome was not formally assessed during this study.

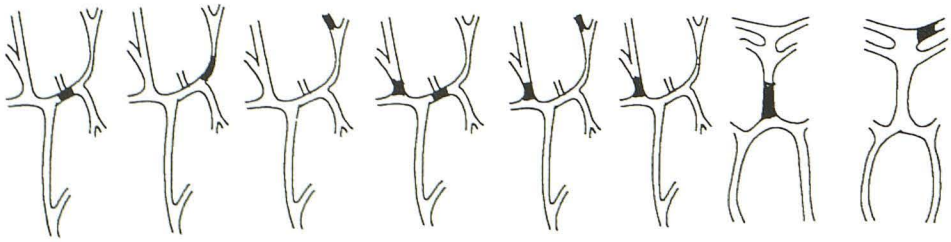
Statistical Analyses

The data are presented in raw form as mean ± standard deviation. Comparisons between the differences in the nominal data sets were made by Fisher's exact test and the Yates corrected χ^2 test (Tables 3, 5–8). Values <0.05

TABLE 2: Distribution of occlusions, recanalizations, and hemorrhagic transformations



No.	10	11	1	1	1	1
R	2a	0	1b	0	1c	1d
PH		2C				
		1B				
HI	1C					
	2B	1B				



No.	33	14	15	2	1	1	1	1
R	12	5	7	1e	1f	0	1	0
PH	3C	1C	1C					
	2B	1B						
HI	4C		5C			1C		1C
	4B	1B		1B				

Note.—Key:

R =	recanalization	B =	basal ganglia	d =	anterior cerebral
PH =	parenchymatous hematoma	a =	carotid	e =	MCA stem
HI =	hemorrhagic infarction	b =	division	f =	anterior cerebral and branch
C =	cortical	c =	posterior cerebral		

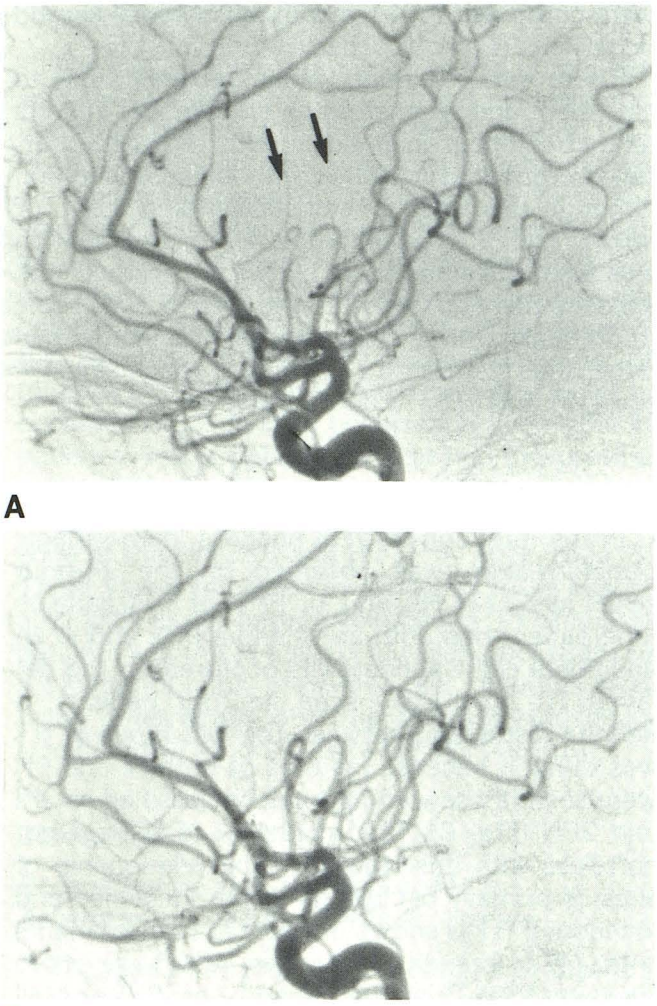


Fig. 3. On the pre-rt-PA infusion (*A*) note the occlusion of both the operculofrontal and central sulcus branches of the middle cerebral artery (*arrows*). On the post-rt-PA infusion angiogram (*B*) the central sulcus branch has completely recanalized but the operculofrontal branch remains occluded. Since not all the branches of the middle cerebral artery were completely recanalized after therapy, the case is classified as a partial recanalization.

TABLE 3: Comparison between recanalizations of arteries in patients with extracranial carotid occlusions, and those with occlusions of any intracranial artery, occlusions of MCA branches, occlusions of MCA divisions, and occlusions of MCA stems

Arteries Occluded	Recanalization	No Recanalization	n	
Extracranial carotid artery	2	21	23	
Any intracranial artery	30	40	70	$P = .006$
MCA branches	8	9	17	$P = .016$
MCA divisions	6	9	15	$P = .057$
MCA stems	13	32	45	$P = .117$

were considered statistically significant. Comparisons between the differences in the continuous data sets were made using a Student t test (Tables 4 and 8). $2P$ values $<.05$ were considered statistically significant.

Results

Arterial Recanalization

Post-rt-PA angiograms demonstrated partial recanalization in 28 and complete recanalization

TABLE 4: Relationship between size of infarcts, recanalized arteries, and hemorrhagic infarcts (analysis A: n = 84; analysis B: n = 71)

	Size (cm^3)	SD	n
A. Recanalization	54.4	64.2	29
No recanalization	90.4	84.0	55
	$P = .047$, $2P = 0.094$		
B. Recanalization	56.7	66.9	26
No recanalization	82.2	80.3	45
	$P = .177$, $2P = 0.354$		
A. HI	76.3	62.2	21
No HI	78.6	84.6	63
	$P = .91$, $2P = 1.82$		
B. HI	77.6	65.9	18
No HI	71.2	79.9	53
	$P = .761$, $2P = 1.5$		

TABLE 5: Relationship between presence of early signs of ischemia, hemorrhagic transformation, and size of infarcts on 24-hour CT scans

	Early ischemia	No early ischemia	
HT	13	19	
No HT	16	45	$P = .235$
Size of infarct (cm^3)	121.5	57.4	
SD	92.9	62.8	
n =	27[a]	57[a]	$P = .0003$

[a] Nine patients with PH excluded.

TABLE 6: Relationship between time to treatment and hemorrhagic transformation

	Before or at 6 hours	After 6 hours	
PH	5	6	
HI	10	11	
No HT	46	15	$P = .012$

TABLE 7: Relationship between recanalization and hemorrhagic transformation

	Recanalization	No Recanalization	n
HT	13[a]	19[b]	32
No HT	19	42	61
			$P = .49$

[a] PH 3; HI 10.
[b] PH 8; HI 11.

TABLE 8: Relationship between the hyperdense MCA sign, recanalization of the MCA stem or division, hemorrhagic transformations, and infarct size in patients with angiographically documented occlusions of the MCA stem or divisions

	Hyperdense MCA	No Hyperdense MCA	
MCA occlusions	16	44	
Recanalization	2	15	
No recanalization	14	29	$P = .188$
HT	6[a]	14[b]	$P = .918$
Size of infarcts	116	65.6	
SD	82.6	79.6	
n =	15[c]	39[c]	
	$P = .046$, $2P = 0.092$		

[a] 5 HI, 1 PH.
[b] 9 HI, 5 PH.
[c] Patients with PHs excluded (see text).

of occluded arteries in four of 93 patients. In one patient, an inferior division of the MCA remained occluded on the immediate post-rt-PA angiogram, but recanalized completely on a 72-hour angiogram. In two patients, partial recanalization of arteries completely occluded on the immediate post-rt-PA films were seen on 90-minute and 3-week angiograms, respectively.

The incidence of recanalization did not increase with increasing doses of rt-PA (1) and, therefore, in the following analyses the recanalization data for all the patients are combined. The relationship of recanalized arteries to the sites of occlusions is displayed in Table 2. As previously noted (1), when each patient was classified according to the most proximal occluded artery (even if multiple occlusions in that same distal territory were present), recanalization occurred in extracranial arteries in 2 of 23 patients (8%), and in intracranial arteries in 30 of 70 patients (41%). Complete recanalization occurred in two patients with branch occlusions, as well as in single patients with division and distal MCA main stem occlusions. The remainder of the recanalizations were partial. A statistically significant increased incidence of recanalized arteries was seen when patients with all types of intracranial occlusions were compared with those with extracranial carotid occlusions ($P = .006$), and specifically when patients with MCA branch occlusions were compared with those with extracranial carotid occlusions ($P = 0.016$; Table 3). An increased recanalization frequency was observed when patients with division occlusions were compared with those with extracranial occlusion ($P = .057$), but not when patients with MCA stem occlusions were compared to those with extracranial carotid occlusions ($P = .117$, Table 3).

There was no relationship between time to treatment and recanalization (1). Smaller infarcts tended to occur in patients with recanalized arteries compared to those without recanalization although this was not statistically significant. ($P = .047$ and $2P = 0.094$; Table 4). This association was also not statistically significant in the MCA subset patients ($P = 0.177$ and $2P = 0.354$, Table 4). Patients with CT signs of early ischemia had larger infarcts than those without those signs ($P = .0003$ and $2P = 0.0006$, Table 5).

Hemorrhagic Transformation

In the intention-to-treat analysis, hemorrhagic transformation was observed on the 24-hour scans in 32 (21 HIs and 11 PHs) of 104 patients (one patient had both an HI and a PH), and in an additional eight patients HIs occurred on the delayed 10- to 14-day scan. In four patients, a definite distinction between the two types of HT was difficult because features of both HI and PH were seen; these were ultimately classified as 2HI and 2PH (Fig. 2). The incidence of HT did not correlate with dose-rate (1). The relationship of sites of primary occlusions to the incidence and location of HT is shown in Table 2. In the patients with MCA branch occlusions, HIs were more frequent than PHs (six HIs and one PH) and all were located in the cortex. In patients with primary occlusions in other locations, the incidence of the two types of HT was less discrepant (15 HIs and 10 PHs). Twelve of these transformations occurred in the cortex, and 13 occurred in the basal ganglia. All PHs occurred in the distribution of the occluded arteries, except in two patients where PHs occurred at sites distant from the original infarcts (one in the opposite occipital lobe and one in the cerebellar hemisphere (Fig. 2)).

Patients treated before or at 6 hours had significantly fewer HTs than those treated after 6 hours ($P = .012$, Table 6) (1). There was no relationship between the presence of early ischemic signs and the subsequent development of HT ($P = .235$, Table 5), or between the size of the established infarct on the 24-hour scan and the presence of HI ($P = 0.91$, $2P = 1.82$) for total series; $P = .761$, $2P = 1.5$ for MCA subset series, Table 4). The relationship between recanalization and hemorrhagic transformation was also explored (Table 7), and no association was found ($P = .49$).

Significance of HMCAS

The HMCAS was seen in 16 of the 60 patients with angiographically documented occlusions of the MCA stem (12 of 43) or MCA division (four of 17). The sign was not seen in any patient without a documented occlusion of the MCA stem or division nor were any false positive signs found. Thus the sign had a 100% specificity, but only a 27% sensitivity. There was no apparent correlation between the presence (or absence) of the sign and subsequent recanalization at 60 minutes ($P = .188$, Table 8). Recanalization of an occluded MCA division occurred in one of the 16 patients. In this patient the sign had disappeared on the 24-hour CT scan.

There was no relationship between the presence of the HMCAS and HT ($P = .918$, Table 8). There was a trend for the HMCAS to be associated with larger infarct volumes in 15 of the 54 patients with MCA stem or division occlusions (in six patients, PHs prevented the volumes from being determined) but this was not statistically significant ($P = .046$, $2P = 0.092$, Table 8)).

Discussion

Recanalization and Its Relationship to Atherothrombotic and Embolic Stroke

The goal of thrombolytic therapy is to promote reopening of obstructed arteries as soon as possible after the occlusive event to establish blood flow to the ischemic brain tissue. Experience with thrombolytic therapy for stroke beyond 24 hours has shown little benefit for return of neurologic function (5). We have shown that partial (n = 28) or complete (n = 4) recanalized arteries occurred in 32 of 93 patients (34%) (1). The premature termination of this study may partially explain the failure to establish a dose of intravenously administered rt-PA that would result in complete lysis of a significant number of the documented occlusions within 60 minutes. Two of 23 patients (13%) had recanalization of arteries in the extracranial circulation, and 30 of 70 patients (41%) had recanalization of arteries in the intracranial circulation. Our results (1) are consistent with other studies of patients treated with intravenous rt-PA after acute embolic stroke in which an average recanalization of 40% of occluded arteries was found (6–8). Mori and colleagues also reported that MCA occlusions recanalized more frequently than internal carotid occlusions (9), confirming our observation that, after the 60-minute rt-PA infusion, distal occlusions were more likely to recanalize than proximal occlusions. It is possible that access of the agent to the smaller distal thrombus located intracranially was more effective than to proximally located large extracranial carotid artery thrombi. In the latter case, stagnant flow in the long segment of the carotid artery and absence of collaterals may have restricted access to rt-PA. Furthermore, resistance of large atheromatous-based extracranial thrombi to rt-PA therapy compared to smaller occlusions of the intracranial arteries may have contributed to the observations.

In the natural course of events, embolic material is believed to fragment, migrate distally, and often lyse completely, thereby contributing to spontaneous recanalization (10). The current study provides information on arterial patency very early after symptom onset, which is consistent with previous published reports (9, 11–13) suggesting increased patency with time from ictus. In any given patient however, the contribution of spontaneous recanalization can only be confirmed by a placebo-controlled angiographic study (11–14).

Hemorrhagic Transformations and Their Relationship to the Natural History of HTs following Embolic Stroke

Hemorrhagic transformation was observed in 32 of the 93 patients (34%) on the 24-hour CT scans. The incidence of HT reported in other studies of carotid territory acute stroke treated with fibrinolytic agents is between 7% and 53% (7–9, 15). The majority of the hemorrhagic events described were HIs. In this series, the presence of an HI was not usually associated with adverse clinical events, but clinically significant complications often occurred in patients with PH (1). We also noted that both HIs and PHs were associated with a significantly later time to treatment from stroke onset (1).

Hemorrhagic transformation is a natural and common tissue accompaniment of embolic infarction (16). Autopsy studies have shown that HI occur in 51% to 71% of patients dying from embolic strokes (10, 17–19). A recent CT study in patients with cardio-embolic stroke showed HI in 41% of patients (14). Hornig et al found HI or PH in 43% of patients studied by serial CT scans (20). Despite numerous unaccounted variables in literature reports, ie, the use of anticoagulant therapy, embolic versus atherothrombotic stroke,

the time elapsed from the onset of the stroke (14, 20–24), the incidence of HI in this series (21 of 93 patients; 22%) does not appear to exceed the natural history of embolic stroke.

Hemorrhagic transformation has been attributed to leakage from smaller vessels following recanalization of an occluded feeding artery (10, 12). However, the finding of HT with persistent occlusion of the primary artery (25) has suggested that hemorrhage may also occur from other vascular sources such as leptomeningeal collateral channels. In this study, the number of patients with recanalization of large arteries and subsequent HT (13 of 22, 40%) was not substantially different from the number of patients without recanalization, but with subsequent HT (19 of 42, 30%). Because recanalization was assessed at 1 hour and HT at 24 hours following initial angiography, recanalization of previously occluded arteries could have occurred after the initial posttherapy angiogram.

In two studies, the incidence of HI was maximal in the second week after ictus (14, 26). Delayed HIs (which could have occurred anytime after 24 hours) were noted in eight patients on the 10 to 14-day scans. However, none were symptomatic. One explanation for delayed HI is resolution of the edema within the infarct permitting reperfusion of vessels in the region surrounding the infarct, and diapedesis of blood through damaged vessel wall (20). HI has also been attributed to large infarct size in several reports (14, 20, 27, 28). We could not confirm a relationship between the size of the infarct on the 24-hour scan and the development of HI. In some patients with delayed HIs, contrast-enhanced scans demonstrated enhancement patterns that precisely followed the configuration of the high-density lesions on the previous nonenhanced scans. In those patients, HI may have been due to a break in the blood-brain barrier that occurs in the second week after cerebral infarction (26).

The incidence of spontaneous PH is less than that of HI in nonanticoagulated patients following cerebral embolism (14, 28, 29). These findings compare favorably with the 11 of 104 patients (10.6%) in the intention-to-treat analysis (1).

In only two patients did PH occur distant from the infarct. Occlusions in cortical branches were associated with HT in the same territory, and more proximal occlusions (MCA division and stem) were associated with hemorrhage equally distributed between the cortex and the basal ganglia. Similarly in patients with internal carotid artery occlusions and presumed MCA territory embolism, HT occurred in both the basal ganglia and in the cortex. These findings agree with those of Okada and colleagues who found that in the natural history of embolic stroke, except in the case of distal branch occlusions, there is no significant difference in the location of HI among the different vascular territories (14).

Predictive Value of the Entry Scan for Hemorrhagic Transformation

The findings of early ischemia on CT performed soon after embolism is reported to be predictive for HT (24). Early ischemia was seen in 29 of our 93 patients (31%), a lower incidence than that reported by Bryan and coauthors (58% within 24 hours) and Tomura and colleagues (92% within 4 hours of the stroke) (30, 31). Our low detection rate could be attributed to the variety of scanners of different vintages used in the present study. No relationship between early signs of cerebral ischemia and HT was noted, but the finding that early ischemia was accompanied with larger infarcts suggests that the sensitivity of CT for signs of early ischemia is dependent on the size of the developing infarct.

HMCAS have been reported as the harbinger of a large infarct and may be predictive for the development of HT (3). The sign was observed in 27% (16 of 60 patients) with documented occlusions of the MCA or its divisions. This is less than the 50% prevalence (18 of 36 patients) with acute stroke and angiographically documented occlusions of the terminal carotid artery, the carotid siphon, or the main stem of the MCA reported by others (32). That the HMCAS is not seen in all patients with angiographically proven occlusions of the proximal MCA illustrates the limitation of the sign for patient selection. We also found the sign more frequently in patients who developed large infarcts than in those who developed small infarcts (33, 34) but the association was not significant at the 2*P* value. We could not confirm the observation of a relationship between the presence of a HMCAS and HT.

Relationship between Recanalization and Infarct Size

In the setting of an acute stroke, the relationship of recanalization to later infarct size on CT was examined by Mori and colleagues in an intraarterial urokinase study (36). They found that

in patients with MCA occlusions the infarcts assessed 3 days after treatment were smaller in patient with recanalized arteries. In the 84 patients in the present study in whom infarct size could be determined, recanalization was also seen with small infarcts but the association was not significant at the 2*P* value. This association could not be confirmed in the subset of 71 patients with MCA occlusions alone. An association between recanalization and the development of a small infarct would suggest that distal artery occlusions are more likely to recanalize and lead to small infarcts. Others have suggested that a combination of rapid recanalization together with good leptomeningeal collaterals significantly reduces the size of the infarcts (36). Whether microvascular patency is affected by the use of thrombolytic agents is not known.

Limitations of This Study

Documented occlusion of a brain supplying artery that could account for the neurologic deficit and the absence of intracerebral hemorrhage was required for a patient to be treated with rt-PA in this study. Unfortunately, documentation of an occlusion by angiography is time-consuming. The mean time from patient entry to initiation of the rt-PA was 5.4 ± 1.7 hours for all patients treated. In the future, magnetic resonance (MR) angiography, if carried out safely with adequate monitoring on unstable patients, may obviate the need for CT scans and cerebral angiography and decrease the time to diagnosis. Standard spin-echo imaging after paramagnetic contrast administration has been shown to be sensitive to slow arterial flow (37, 38) and can show arterial enhancement within 2 hours of the clinical onset of the stroke (38). With present technology, MR cannot diagnose early hemorrhage. MR angiography will also have to become as reliable as conventional angiography in the diagnosis of intracranial vascular occlusions.

The leptomeningeal collateral channesl were not assessed in this study. Therefore, we cannot determine whether such anastomoses may have influenced infarction size, recanalization, or hemorrhagic transformation.

Safety of Cerebral Angiography in Acute Embolic Stroke

Angiography can be safely carried out in patients with acute stroke (1). Early studies on the safety of cerebral angiography in patients with acute stroke have indicated an increased risk in the acute phase as compared to those studied later when percutaneous carotid techniques were used (39, 40). Earnest and colleagues reported a 4.2% incidence of complications among 637 angiograms carried out for cerebrovascular disease using transfemoral catheter techniques. Among the complications, 34% were transient (<24 hours), 0.2% were reversible (>24 hour, <7 days), and 0.6% were permanent (41). Patients with recent stroke (< 30 days) as well as frequent transient ischemic attacks (>1/day) had a significant increase in the incidence of neurologic complications. In a separate study, Faught and coworkers stated that "neither patients with acute deficits (< 24 hours), nor those with severe deficits suffered an increased rate of cerebral complications" (42). Data from this study supports this latter finding; in no patient did the first pretreatment angiogram cause any neurologic deficit, although in two patients extracerebral hemorrhagic complications occurred that may have been augmented by the rt-PA. In addition, one patient had a new neurologic deficient during the first post-rt-PA angiogram in the territory contralateral to the entry symptoms. Femoral hematomas, one severe necessitating a blood transfusion, and 11 classified as moderate not needing transfusions occurred at the femoral artery puncture site and were reasonably attributed to the puncture. Femoral sheaths were used in 11 of these 12 cases. Three other groin hematomas, attributed to previous femoral vein punctures also occurred.

This experience illustrates that valuable information may be obtained by the use of neuroradiologic techniques in trials of fibrinolytic therapy. Of the initial 139 patients in whom occluded arteries were suspected, occlusions were actually found in 112 (82%) supporting the clinical accuracy of diagnosis in this study. The vascular information and the recanalization response data suggest that factors including the dose-rate, occlusion location, vessel size, the presence of HMCAS, and perhaps the mode of delivery may be important in recanalization efficacy. Although not addressed in this study, the use of new techniques such as MR angiography and/or transcranial doppler sonography may provide important vascular information and reduce the time to treatment. Further studies with placebo controls will be necessary to clarify these issues.

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Appendix A

Hemorrhagic infarct (HI)—areas of barely visible increased density with indistinct margins within an infarct, or areas of increased density with indistinct margins and a speckled or mottled appearance and/or multiple areas of coalescent hemorrhage. A mass effect could be present due either to the edema or to the hemorrhagic component.

Parenchymatous hematoma (PH)—very dense, homogenous region(s) of circumscribed increased density usually with mass effect.

The CT scan distinction between a severe hemorrhagic infarction and a parenchymatous intracerebral hematoma

was not always possible and in four cases a category of indeterminate hemorrhagic transformation was used. Two of these indeterminate cases are ultimately classified as hemorrhagic infarcts and two as hematomas.

Appendix B

Grade 0—No perfusion

Grade 1—Penetration with minimal perfusion where the contrast passes beyond the area of obstruction but "hangs up" and fails to opacify the arterial bed distal to the obstruction.

Grade 2—Partial perfusion where the contrast passes beyond the area of obstruction but its rate of clearance from the distal bed is perceptibly slower than that of comparable normal arteries.

Grade 3—Complete perfusion where the antegrade flow into the arterial bed distal to the obstruction occurs as promptly as through uninvolved arteries.

In this study the following definitions were used:

No recanalization—grade 0 or grade 1 perfusion.

Partial recanalization—an improvement from grade 0 to 2 of all or of single arteries in cases with multiple vessel occlusions. (*Note*: The clinical outcome was not considered a factor in these analyses. The partial perfusion definition applied even if an artery opened up after treatment but an arterial division or some branches remained occluded.)

Complete recanalization—grade 3 perfusion.

Note: The above definitions applied when any artery in a vascular distribution showed improved perfusion.

BOOKS RECEIVED

Fundamentals of Neuroimaging. By William W. Woodruff. Philadelphia: WB Saunders, 592 pp, 1993. $95

Brain Surgery: Complication Avoidance and Management. Edited by Michael L. J. Apuzzo. New York: Churchill Livingstone, Vol. 1: 139 pp, Vol. 2: 139 pp, 1993. $475 for two-volume set

Leonardo da Vinci: The Anatomy of Man. By Martin Clayton. Boston: Little, Brown, and Company, 141 pp, 1992. $40

Gamuts in Radiology. By Maurice M. Reeder and William G. Bradley, Jr. New York: Springer-Verlag, 686 pp, 1993. $79

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Errata

The following are corrections to the January issue article "Neuroradiologic Evaluation of Patients with Acute Stroke Treated with Recombinant Tissue Plasminogen Activator," Wolpert SM, Bruckmann H, Greenlee R, et al., *AJNR: Am J Neuroradiol* 1993;14:3–13:

On page 3, line 10 of the abstract should read "The presence of a HMCAS was 100% specific for an occluded artery. . . ."

On page 11, line 25 of the second column, the word "deficient" should be "deficit."

On page 13, line 10 of the second column, the word "perfusion" should be "recanalization."