Existence of the Diffusion-Perfusion Mismatch within 24 Hours after Onset of Acute Stroke: Dependence on Proximal Arterial Occlusion[1]

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Purpose: To assess the existence of a mismatch between lesions on diffusion-weighted (DW) and perfusion-weighted (PW) magnetic resonance (MR) images obtained within 24 hours after onset of acute stroke and to use mismatch data and angiographic evidence of proximal arterial occlusion (PAO) to investigate whether the existence of the mismatch depends on the existence of PAO.

Materials and Methods: In this institutional review board–approved, HIPAA-compliant study, 109 retrospectively identified patients had undergone DW and PW imaging within 24 hours of stroke onset. Relative mismatch was computed as the difference between lesion volumes on mean transit time maps and DW images, divided by DW lesion volume. Computed tomographic (CT) angiography or MR angiography distinguished patients with PAO (n = 68) from those with no PAO (NPAO; n = 41). Eligibility for hypothetical thrombolysis was assessed with two different criteria: *(a)* one derived from the successful Desmoteplase in Acute Ischemic Stroke Trial (DIAS) and Dose Escalation of Desmoteplase for Acute Ischemic Stroke Trial (DEDAS), and *(b)* another requiring 160% mismatch.

Results: Of the 109 patients, 77 (71%) satisfied the DIAS-DEDAS eligibility criteria, and 61 (56%) satisfied the 160% criterion. The NPAO patients demonstrated decreasing eligibility with increasing time after onset by using DIAS-DEDAS criteria (P = .015) and showed a similar trend with the 160% criterion (P = .078). The NPAO patients were less likely to be eligible after 9 hours than before 9 hours (17% for >9 hours vs 72% for <9 hours with DIAS-DEDAS criteria, P = .002; and 8% for >9 hours vs 45% for <9 hours with 160% criterion, P = .033). However, PAO patients demonstrated a trend toward increasing eligibility with the DIAS-DEDAS criteria (P = .099) and no significant difference for after 9 hours versus before 9 hours (84% for >9 hours vs 78% for <9 hours with DIAS-DEDAS criteria, P = .742; and 68% for >9 hours vs 69% for <9 hours with 160% criterion, P > .999).

Conclusion: Persistence of mismatch after 9 hours is common and occurs most often in patients with PAO.

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Intravenous thrombolytic therapy improves outcomes in patients with acute stroke (1) but is administered in only 1%–7% of cases (2–6). Most patients are deemed ineligible for thrombolysis because they present later than 3 hours after they were last seen without symptoms, a time limit that is imposed by current treatment requirements (7,8) on the basis of one early trial that showed a clinical benefit when thrombolysis was initiated within the 3-hour window (1) and on the basis of other early trials that showed worse clinical outcomes when the treatment window was extended to 5 or 6 hours (9–11). Underlying the 3-hour limit are the suppositions that *(a)* patients imaged later than 3 hours may have less to gain from thrombolysis because they may have a smaller volume of hypoperfused brain tissue that is at risk for infarction but is still salvageable, and *(b)* thrombolysis may be riskier in these patients because more-advanced ischemic damage may mean a greater likelihood of intracranial hemorrhage after treatment. Many more patients could receive this potentially lifesaving therapy if it were approved for use outside the 3-hour window.

In several studies, investigators have shown that in some patients, intravenous thrombolysis can be safe and effective as long as 6 hours (12) or 9 hours (13,14) after symptom onset. In these studies, patients were eligible for thrombolysis if they demonstrated a sufficient volume of brain tissue that was considered to be threatened by ischemia but still potentially salvageable, as manifested by at least a 20% (13,14) or 50% (12) mismatch between lesions seen on diffusion-weighted (DW) and perfusion-weighted (PW) magnetic resonance (MR) images. These criteria were based on the assumptions that tissue that is abnormal on DW images is irreversibly damaged and will not benefit from reperfusion, whereas additional DW-normal but PW-abnormal tissue is hypoperfused and at risk for infarction but is still potentially salvageable by timely reperfusion. These successful applications of the diffusion-perfusion mismatch in extending the time window for thrombolysis to 9 hours raise the possibility that thrombolysis could be performed even later than 9 hours if patients continue to demonstrate mismatch after that time.

In several small studies, investigators have demonstrated that some patients do continue to demonstrate a mismatch after 10 hours (15) or within 24 hours (16,17) of stroke onset. In the current study, we sought to use a larger sample of patients *(a)* to obtain a better estimate of the prevalence of the diffusion-perfusion mismatch during the first 24 hours and *(b)* to assess whether a substantial proportion of patients imaged later than 9 hours after stroke onset could be eligible for thrombolysis if thrombolysis were to be made available to them on the basis of the existence of a mismatch.

In such patients, the decision of whether to administer intravenous or intra-arterial thrombolysis may depend on the specific artery that is occluded because intra-arterial therapy may have a greater chance of success in recanalizing occluded proximal arteries (18–23), whereas intra-arterial therapy cannot be considered when no proximal occlusion is present. Therefore we used computed tomographic (CT) angiographic

Advances in Knowledge

- Intravenous thrombolysis can be lifesaving for acute stroke patients but is currently available to only the small minority of patients who present less than 3 hours after symptom onset.
- Some recent studies have shown that intravenous thrombolysis can be safe and effective as long as 9 hours after onset when diffusion- and perfusion-weighted MR images were used to select only those patients with a sufficiently large diffusion-perfusion mismatch, and therefore a large quantity of brain tissue that is putatively salvageable but at risk for infarction.
- The findings of this study show that a substantial percentage of stroke patients continue to demonstrate a diffusion-perfusion mismatch after 9 hours, to as long as 24 hours after symptom onset, but that the existence of a mismatch after 9 hours is more likely in patients with a proximal arterial occlusion (PAO) than in patients without a PAO.

Implication for Patient Care

- The current findings may help to motivate future trials of intravenous thrombolysis in patients with a diffusion-perfusion mismatch who present more than 9 hours after stroke onset; and for institutions that cannot currently perform DW and PW imaging of acute stroke patients, the findings suggest that patients who are imaged after 9 hours and have proximal arterial occlusions seen on CT angiographic or MR angiographic images may be more likely to have a clinically important quantity of persistently threatened but salvageable brain tissue, and therefore may be more likely to benefit from thrombolysis or other therapeutic intervention.

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Abbreviations:
DEDAS = Dose Escalation of Desmoteplase for Acute Ischemic Stroke Trial
DIAS = Desmoteplase in Acute Ischemic Stroke Trial
DW = diffusion-weighted
MTT = mean transit time
NPAO = no proximal arterial occlusion
PAO = proximal arterial occlusion
PW = perfusion-weighted

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images and MR angiographic images to divide our patients into those who did and did not demonstrate evidence of proximal arterial occlusion (PAO) and to investigate whether the existence of the mismatch depends on the existence of PAO.

Materials and Methods

Patient Selection

This study was compliant with the Health Insurance Portability and Accountability Act (HIPAA) and was approved by our institutional review board, which waived the requirement for informed consent because only a retrospective review of patient records was performed. We retrospectively identified all patients who came to the emergency department of our hospital from June 2005 through December 2006 with symptoms suggestive of recent stroke. Patients were included in this study if they had undergone a DW imaging examination that demonstrated a recent anterior circulation infarct, as well as PW imaging, and either CT or MR angiography of the head, all performed within 24 hours of the time when each patient was last known to be without new symptoms. The interval between that time and the time of MR imaging was considered the time since stroke onset. Patients who had received any thrombolytic agent prior to imaging were excluded.

Imaging

Patients underwent MR imaging on a 1.5-T imager (GE Medical Systems, Milwaukee, Wis). For 96 patients, the standard MR protocol of our department was used. This included a DW imaging sequence with two 180° radiofrequency pulses to reduce eddy-current–induced distortions (24). Repetition time was 5000 msec. Minimum echo time was used, typically 85–110 msec. Transverse images were acquired with a section thickness of 5 mm and a 1-mm intersection gap. The field of view was 22 cm, with a 128 × 128 matrix, zero-filled to 256 × 256. As many sections as needed to image the entire brain were acquired. For each section, high-gradient-factor (b = 1000 sec/mm^2) images were acquired in each of six directions, with an additional image acquired without diffusion gradients (b = 0 sec/mm^2). This sequence was repeated five times, so that 35 images were acquired for each section, which resulted in a total imaging time of 3 minutes 5 seconds.

The PW imaging sequence used in our standard MR protocol was a gradient-echo echo-planar sequence (1500/40 [repetition time msec/echo time msec]). The field of view, section orientation, thickness, and spacing were as in the DW imaging sequence described previously, with a matrix of 128 × 128. Sixteen sections were acquired at each of 46 time points, which resulted in an imaging time of 1 minute 5 seconds. After a 10-second delay before injection, 20 mL of gadopentetate dimeglumine, 0.5 mol/L (Magnevist; Bayer HealthCare, Leverkusen, Germany), was injected at 5 mL/sec through a peripheral intravenous catheter by using a power injector (Medrad, Indianola, Pa), followed by a 20-mL physiologic saline flush injected at the same rate.

Maps of mean transit time (MTT) were computed by using singular value decomposition deconvolution (25). The MTT was used rather than either of the other two most commonly used perfusion metrics—*(a)* time to peak signal change or *(b)* the time at which the deconvoluted tissue residue function reaches its maximum—for several reasons. First, MTT was the metric used in two successful trials, the Desmoteplase in Acute Ischemic Stroke Trial (DIAS) and the Dose Escalation of Desmoteplase for Acute Ischemic Stroke Trial (DEDAS), although in another successful trial of thrombolysis after more than 3 hours, the time to peak signal change was used (12). Also, of these three metrics, MTT may have the most direct physiologic relation to tissue survival because oxygen extraction is diffusion limited in brain capillaries and therefore determined by vascular transit time (26,27). In contrast, the time at which the deconvoluted tissue residue function reaches its maximum is a measure of the time at which injected contrast material arrives in a particular brain voxel, which is abnormal in collaterally perfused tissue even when blood flow is normal (28). Similarly, time to peak signal change is dependent on a number of different fac-

Figure 1

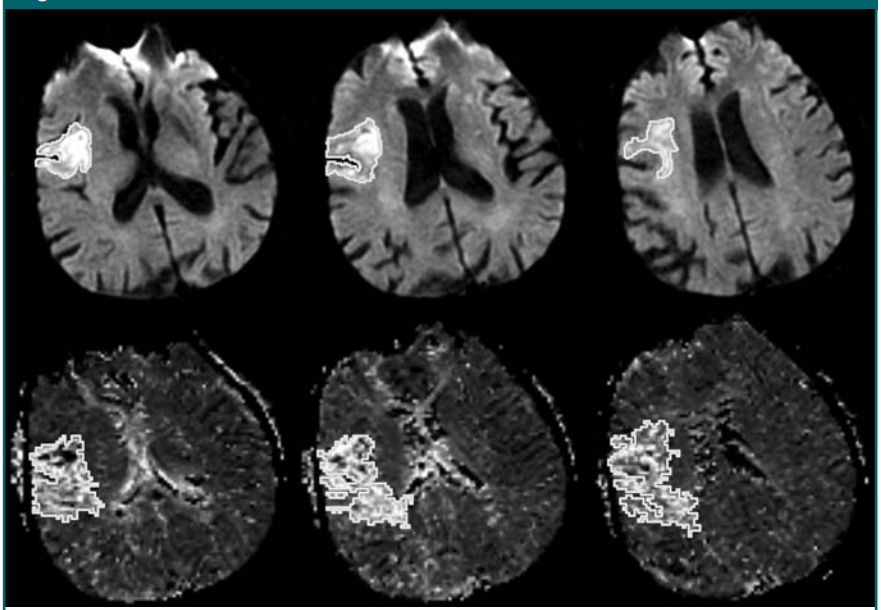

Figure 1: Diffusion-perfusion mismatch in a 76-year-old man imaged 5.7 hours after onset of left-sided weakness and dysarthria. Top row: Selected transverse DW images (5000/88.9, 90° flip angle). Bottom row: MTT maps. Measurement of the volumes of the lesions, only portions of which are shown here, demonstrated a 340% diffusion-perfusion mismatch.

tors, including MTT, bolus arrival time, and regional blood flow (29).

For the above patients imaged with standard departmental protocol, MR angiographic images of the head were acquired without injected contrast material, by using a three-dimensional time-of-flight sequence: 36/6.3, with 25° flip angle, 18-cm field of view, and 512 × 512 matrix. One hundred eleven transverse images were reconstructed with a section thickness of 1.4 mm and spacing of 0.7 mm.

A slightly different MR protocol was used for 13 patients who were participants in a multicenter trial that required standardized imaging parameters. For these patients, the DW sequence used a single 180° radiofrequency pulse, repetition time of 3000 msec, minimum echo time (typically 80–90 msec), 24-cm field of view, 7-mm section thickness with no intersection gap, and diffusion gradients applied in three directions, with an additional image acquired without diffusion gradients. These acquisitions were repeated two times, for a total of eight images acquired per section. For these patients, PW images were acquired with the following pulse sequence: 2050/50, 60° flip angle, 24-cm field of view, 7-mm section thickness with no intersection gap, and 20 sections acquired. The MR angiographic sequence used for these patients included the following: 27/7, 30° flip angle, 22-cm field of view, overlapping 1.4-mm sections with 0.7-mm spacing, and 45–55 sections acquired. Other imaging parameters for these patients were as described previously.

CT angiography was performed following injection of 100–140 mL of iopamidol, 61.2 g/100 mL (Isovue; Bracco Diagnostics, Princeton, NJ), at 3 mL/sec. Imaging began 25 seconds following contrast material injection (40 seconds for patients with atrial fibrillation). Parameters were 140 kVp, 220–250 mA, 0.8–1.0-second rotation time, 2.5-mm section thickness, 1.25-mm reconstruction interval, table speed of 3.75 mm per rotation, 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.

Table 1

Age, Sex Distribution, and Serum Glucose Levels of Patients with and without PAO

Parameter	All Patients	PAO Patients	NPAO Patients
n	109	68	41
Age (y)			
Mean	69.8	70.4	68.9
Median	72.2	75.4	71.2
SD	15.6	17.4	12.4
No. of male patients*	52 (48)	31 (46)	21 (51)
Serum glucose level (mg/dL)			
Mean	132	130	137
Median	121	120	121
SD	45.9	36.2	58.8

Note.—PAO and NPAO patients did not differ significantly with respect to any of these three variables. SD = standard deviation.

* Numbers within parentheses are percentage of male patients in group.

Table 2

Mean Volumes of DW Image Lesions, MTT Lesions, and Mismatch Regions in PAO and NPAO Patients

Variable	Mean Volume (cm^3)			*P* Value*
	All Patients	PAO Patients	NPAO Patients	
DW image lesion	41.5 (65.5)	58.2 (76.0)	13.8 (25.6)	.0005
MTT lesion	112.0 (99.8)	162.6 (92.7)	28.1 (30.9)	<.0001
Absolute mismatch volume	73.2 (71.4)	108.6 (68.3)	14.4 (16.4)	<.0001

Note.—Data within parentheses are one standard deviation.

* *P* value for difference between PAO and NPAO patients. All three volumes were significantly larger in PAO patients than in NPAO patients.

Image Processing

Lesions on DW images and MTT maps were outlined by a neuroradiologist (P.W.S.), with the assistance of a research technologist (Fig 1), using semiautomated software (Analyze 7.0; Analyze Direct, Overland Park, Kan). Neither the neuroradiologist nor the technologist was aware of the time of stroke onset or the locations of arterial lesions. For each patient, the volumes of the MTT and DW lesions were measured, and the absolute volume of the diffusion-perfusion mismatch was calculated as the difference between the two volume determinations. A mismatch volume of zero was recorded for cases in which the MTT lesion was smaller than the DW lesion. We assume that in most cases, this situation would result from spontaneous reperfusion prior to the time of imaging. We base that assumption on the idea that most tissue undergoing infarction was, at some point, underperfused, although there are proposed mechanisms by which infarction might occur in normally perfused tissue adjacent to an ischemic region (30–35). Absolute mismatch volume was divided by DW lesion volume to yield relative mismatch volume, a statistic that raters estimated by visual inspection in assessing eligibility for thrombolysis in DIAS (13) and DEDAS (14).

In a separate session, the neuroradiologist reviewed CT angiographic images for each patient, or MR angiographic images for those seven patients for whom CT angiographic images were unavailable or uninterpretable, and assessed whether there was evidence of

Figure 2

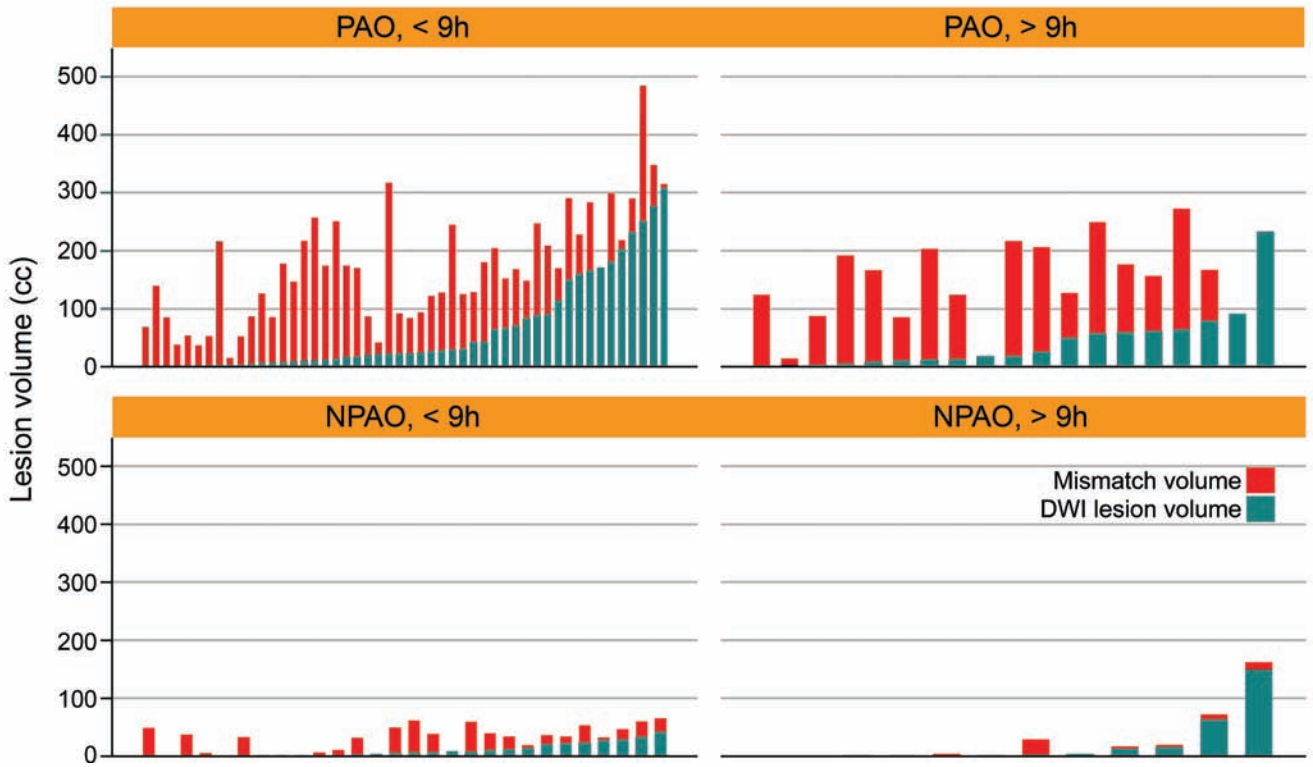

Figure 2: Volumes of DW image (*DWI*) lesions (teal bars) and absolute mismatch volumes (red bars) for every patient in study. Because absolute mismatch volume is defined as the difference between the MTT and DW lesion volumes, the combined height of the teal and red bars for each patient represents the volume of the MTT lesion. Note the larger size of DW lesions, MTT lesions, and absolute mismatch volumes seen in PAO patients (top row) compared with those seen in NPAO patients (bottom row). Note that bars are evenly spaced, but some are so small as to be difficult to see.

occlusion of an artery that could be responsible for the patient's infarct. Stenotic lesions without frank occlusion were not recorded. Occlusive lesions in an internal carotid artery, an M1 middle cerebral artery segment, an A1 anterior cerebral artery segment, or the proximal portion of an M2 middle cerebral artery segment or an A2 anterior cerebral artery segment were designated as PAO. The time that elapsed between vascular imaging and the earlier of the DW and PW pulse sequences was recorded for each patient.

Statistical Analysis

Patients with PAO were compared to patients with no PAO (NPAO) with respect to age and blood glucose level by using two-tailed t tests and were compared with respect to sex distribution by using a χ^2 test. Two-tailed t tests were used to compare the DW lesion volume, MTT lesion volume, and mismatch volume in PAO patients with these same three volumes in NPAO patients.

We determined whether or not each patient's images would have made him or her eligible for thrombolysis in hypothetical trials by using each of two different criteria: *(a)* DIAS-DEDAS criteria and *(b)* the 160% mismatch criterion. In the first, we used a multifactorial set of imaging criteria that were based on those used in the DIAS and DEDAS studies. These criteria included a relative mismatch volume measuring at least 20%, an MTT abnormality that included cortical gray matter and measured at least 4.19 cm^3 (corresponding to a sphere with a diameter of 2 cm, the minimum lesion diameter specified in DIAS and DEDAS studies), as well as a DW image abnormality measuring no larger than 100 cm^3 in volume. Gradient-echo susceptibility-weighted images were not available for all patients and were not included in this study.

Note that in addition to the previously specified image-based criteria, the DIAS and DEDAS studies included clinical criteria, notably the National Institutes of Health Stroke Scale (NIHSS) score. We did not include clinical criteria in our determinations of hypothetical eligibility because not all relevant clinical data were available in all patients' medical records and because excluding patients for whom such records were unavailable could have unduly biased the composition of our sample.

In addition to the DIAS-DEDAS criteria, we also determined patient eligibility for hypothetical thrombolysis with a second criterion: the 160% mismatch criterion. We determined whether each patient's relative mismatch volume measured at least 160%, an alternative threshold that has been suggested by a reanalysis of the data

from the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study (36) as the best threshold for predicting a favorable response to reperfusion.

Logistic regression was used to determine whether each group of patients (PAO and NPAO) demonstrated increasing or decreasing likelihood of eligibility for thrombolysis with increasing time since stroke onset, by using each of the two criteria for thrombolysis (DIAS-DEDAS and 160%). Two two-sided Fisher exact tests were used to assess whether PAO patients and NPAO patients, respectively, were less likely to meet each of the two criteria for hypothetical thrombolysis more than versus less than 9 hours after stroke onset. Two more two-tailed Fisher exact tests were used to assess whether, among patients imaged after 9 hours, the PAO and NPAO patients had different likelihoods of meeting criteria for hypothetical thrombolysis.

Results

One hundred nine patients were included in this study. For the seven patients who did not undergo CT angiography during their visits to the emergency department, arterial patency was assessed with MR angiographic images, which were acquired during the same examination as the DW and PW images. CT angiography was used for the other 102 patients and was performed after the MR imaging examination in 14 patients and before the MR imaging examination in 88 patients. For those 88 patients, the mean and median elapsed times between CT angiography and DW/PW imaging were 45.9 minutes and 28.0 minutes, respectively.

Of the 109 patients, 68 (62%) were PAO patients, and 41 (38%) were NPAO patients. Sites of occlusion in the 68 PAO patients were distributed as follows: internal carotid artery, 14 (21%); M1 middle cerebral artery segment or middle cerebral artery bifurcation, 35 (51%); and proximal M2 middle cerebral artery segment or segments, 19 (28%). No proximal anterior cerebral artery occlusions were noted. The PAO and NPAO patients did not differ significantly with respect to age ($P = .628$), sex distribution ($P = .569$), or blood glucose levels ($P = .472$), which are summarized in Table 1. Among patients imaged earlier than 9 hours, PAO patients did not differ significantly from NPAO patients with respect to time since symptom onset (means, 4.49 and

Table 3

Proportions of PAO and NPAO Patients Imaged Less than and More than 9 Hours after Stroke Onset Who Satisfied Each of Two Different Eligibility Criteria for Hypothetical Thrombolysis

Patient Group and Criteria*	Time after Stroke Onset (h)		*P* Value†
	<9	>9	
PAO			
DIAS-DEDAS	38/49 (78)	16/19 (84)	.742
160%	34/49 (69)	13/19 (68)	>.999
NPAO			
DIAS-DEDAS	21/29 (72)	2/12 (17)	.002
160%	13/29 (45)	1/12 (8)	.033

Note.—Table data are numbers of patients; numbers within parentheses are percentages.

* Two eligibility criteria are *(a)* a multifactorial set of criteria adapted from the DIAS and DEDAS studies ("DIAS-DEDAS") and *(b)* a simple determination of whether relative mismatch volume measured at least 160% ("160%").

† *P* value for difference between <9 hours and >9 hours.

Figure 3

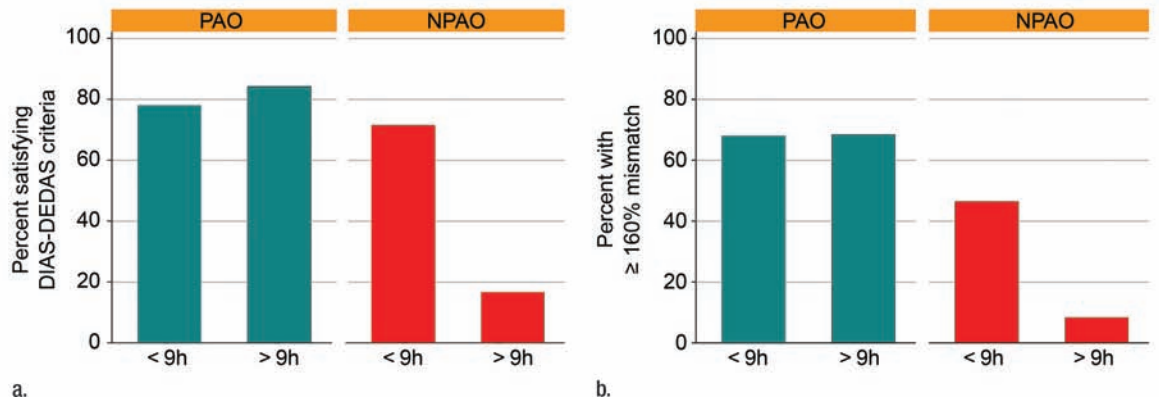

Figure 3: Proportions of PAO patients (teal bars) and NPAO patients (red bars) imaged less than and more than 9 hours after stroke onset who satisfied each of two different criteria for hypothetical thrombolysis: **(a)** a multifactorial set of criteria derived from the DIAS and DEDAS studies, and **(b)** relative mismatch measuring at least 160%. With both criteria, PAO patients were no less likely to be eligible for thrombolysis after 9 hours than before 9 hours, but NPAO patients were less likely to be eligible when imaged later than 9 hours ($P = .002$ for DIAS-DEDAS criteria; $P = .033$ for 160% criterion).

5.16 hours, respectively; $P = .193$). Among patients imaged later than 9 hours, PAO patients also did not differ significantly from NPAO patients with respect to time since symptom onset (means, 15.86 and 14.16 hours, respectively; $P = .273$).

Table 2 summarizes the sizes of DW image lesions, MTT lesions, and mismatch regions in PAO and NPAO patients, without considering time since stroke onset. PAO patients had significantly larger DW lesions ($P = .0005$), larger MTT lesions ($P < .0001$), and larger absolute mismatch volumes ($P < .0001$) than NPAO patients. Figure 2 provides a detailed graphical representation of the DW lesion size and absolute mismatch volume of every patient in this study, divided into four groups by CT/MR angiographic findings (PAO vs NPAO) and time since stroke onset (<9 hours vs >9 hours). This figure illustrates the greater absolute size of DW and MTT lesions and mismatch volumes observed in PAO patients, compared with NPAO patients, in both the pre-9-hour and post-9-hour periods.

Most of the patients met both criteria for hypothetical thrombolysis, including 77 of 109 patients (71%) for the DIAS-DEDAS criteria and 61 of 109 patients (56%) for the 160% criterion. With increasing time since onset, NPAO patients became less likely to be eligible for thrombolysis by using the DIAS-DEDAS criteria (odds ratio, 0.81 hour^{-1}; $P = .015$), and there was a trend toward decreasing eligibility by using the 160% criterion (odds ratio, 0.85 hour^{-1}; $P = .078$). In contrast, PAO patients demonstrated a trend toward increasing likelihood of satisfying the DIAS-DEDAS criteria with increasing time since onset (odds ratio, 1.13 hour^{-1}; $P = .099$), although no such trend was observed by using the 160% criterion (odds ratio, 1.03 hour^{-1}; $P = .564$).

Table 3 lists the proportions of PAO and NPAO patients imaged before and after 9 hours who satisfied both criteria. These proportions are depicted graphically in Figure 3. Among NPAO patients, those imaged earlier than 9 hours were significantly more likely than those imaged later than 9 hours to satisfy thrombolysis criteria ($P = .002$ for DIAS-DEDAS criteria; $P = .033$ for 160% criterion). However, among PAO patients, those imaged earlier than 9 hours were no more likely than those imaged later than 9 hours to satisfy thrombolysis criteria ($P = .742$ for DIAS-DEDAS criteria; $P > .999$ for 160% criterion). Among patients imaged after 9 hours, PAO patients were more likely to satisfy both the DIAS-DEDAS ($P < .001$) and 160% ($P = .002$) criteria.

Discussion

Our results in a larger patient sample confirm earlier findings that the diffusion-perfusion mismatch persists for more than 9 hours after stroke onset in some patients. In one prior study, one of three patients (33%) imaged 10 hours after onset demonstrated at least a 20% mismatch (15). In another study, in which time to peak contrast enhancement was used as the perfusion metric rather than MTT, six of nine patients (67%) imaged between 9 and 24 hours after onset had at least a 20% mismatch (16). In a third study (17), investigators did not report exact lesion volumes but found that seven of 15 patients (47%) imaged between 12 and 24 hours had areas of altered perfusion, manifested by increased time to peak values, that were larger than their lesion in DW images.

Our findings expand on those of prior studies by showing that the existence of the mismatch after more than 9 hours is dependent on the existence of a PAO. This may be because when there is occlusion of a proximal artery, there is a large volume of brain tissue that is perfused by distal collateral vessels, may experience only mild hypoperfusion, and therefore may survive for a relatively long time without undergoing irreversible infarction or becoming abnormal on DW images.

In contrast, NPAO patients probably belong to one of two categories. In some NPAO patients, infarction may be caused by occlusion of distal arteries located so close to the tissue they supply that collateral circulation cannot maintain a state of mild hypoperfusion in a substantial volume of tissue. All of the threatened tissue undergoes infarction quickly, so that any diffusion-perfusion mismatch is no longer present at the time of imaging. In other patients with no visible proximal occlusion, infarction may be caused by emboli that already have disintegrated by the time of imaging, resulting in spontaneous reperfusion and absence of a diffusion-perfusion mismatch.

Previous studies have found that *(a)* as many as 95% of acute stroke patients are deemed ineligible for thrombolysis because they present too long after they were last seen without symptoms (7) and *(b)* in some patients with a diffusion-perfusion mismatch, the 3-hour time window for thrombolysis may be extended to as much as 9 hours without a substantially increased risk of symptomatic intracranial hemorrhage (12–14). In light of the results of these previous studies, the current finding that a mismatch remains present in most patients imaged between 9 and 24 hours after onset suggests that many more patients could benefit from thrombolysis if investigators in future clinical trials can show success in using the mismatch to select patients for thrombolysis after more than 9 hours.

However, the current results do not by themselves establish that thrombolysis would be safe after 9 hours. Even assuming that the mismatch does identify threatened but still-salvageable tissue, it is possible that irreversibly damaged tissue demonstrates a greater propensity for postthrombolytic hemorrhage with increasing time after stroke onset, and this may limit the acceptable time window for thrombolysis, regardless of the extent of still-salvageable tissue (37,38). Particularly in light of this concern about hemorrhage, the findings of the current study may help to motivate future clinical trials in which the time window for thrombolysis is extended for patients with diffusion-perfusion mismatch, but the findings of this study should not by themselves be considered evidence that extending

the time window would be safe or effective, and these findings cannot alter existing treatment requirements for thrombolysis.

Another limitation of our study is its retrospective design. The exact proportion of patients who demonstrate mismatch after more than 9 hours is difficult to estimate on the basis of the current results because our study was a retrospective one. At our institution, most acute stroke patients undergo an MR imaging examination, but some do not, sometimes because of initial clinical manifestations or CT angiographic findings. Additional studies incorporating prospective imaging of patients regardless of early clinical or CT angiographic findings could help to provide a more accurate estimation of the proportion of patients with mismatch.

This study was designed to investigate the real-world potential for thrombolytic treatment after 9 hours on the basis of extrapolation of previously used clinical criteria, not to elucidate the pathophysiologic mechanisms underlying the persistence of the mismatch. For that reason, we followed previous clinical studies by using the time since the patient was last seen at neurologic baseline as the time since stroke onset. In many cases, this time did not correspond exactly to the time since the patient was first noted to have new symptoms, and therefore the actual time since the ischemic event was not known with certainty.

Additional research including only patients for whom this time could be ascertained exactly would allow for more confident inferences regarding stroke pathophysiology and might help to determine which of the current results are due to the brain's responses to ischemia and which are due instead to patterns in patients' presentations for medical care. For example, we found a trend toward increasing likelihood of PAO patients' meeting DIAS-DEDAS criteria with increasing time since stroke onset. If it is presumed that the mismatch reflects threatened tissue, much of which eventually progresses to infarction and therefore becomes abnormal on DW images, then it seems unlikely that the likelihood of any individual patient having a significant mismatch would increase with time.

We hypothesize that this finding may reflect the fact that patients with superior collateral circulation, and therefore a large mismatch, may tend to experience neurologic deficits that are milder at first. For this reason, these patients may tend to delay seeking medical attention until more than 9 hours has elapsed. In contrast, patients with poor collateral circulation, and therefore a small mismatch, may tend to experience more severe neurologic deficits, and therefore may present sooner. In a study including only patients with precisely known times of onset, investigators could test this hypothesis. Incorporating serial images at multiple times would further allow direct testing of the basic hypothesis that DW lesions tend to grow with time to encompass and therefore eliminate the diffusion-perfusion mismatch.

Our finding that the persistence of the mismatch after 9 hours depends on the existence of a PAO suggests *how* these patients might be treated: PAOs respond relatively poorly to intravenous thrombolysis alone (18–23) but are amenable to intraarterial thrombolysis and mechanical disruption, which may be performed by themselves or after initiation of intravenous thrombolysis as a bridging therapy (39–43).

In summary, the major findings of this study are that a majority of PAO patients who were imaged more than 9 hours after onset continued to demonstrate a diffusion-perfusion mismatch, whereas the proportion of NPAO patients demonstrating a mismatch decreased significantly after 9 hours. This finding may serve to motivate future research on the clinical effectiveness of thrombolysis more than 9 hours after stroke onset and suggests that such a trial's likelihood of success might be enhanced by offering definitive therapy in the form of an intraarterial rather than an intravenous agent.

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