NIHSS/EIC Mismatch Explains the $>\frac{1}{3}$ MCA Conundrum

To the Editor:

The controversy about the significance of early ischemic changes (EIC) on CT after acute stroke by von Kummer, Lyden, and Davis and Donnan1−3 nicely summarizes the issues except for what, in my mind, is the most likely explanation for the discrepancy between the NINDS and ECASS conclusions on this subject. I would also like to propose an alternative way of looking at the “more or less than one third MCA territory” controversy.

The aim of treatment with intravenous tPA is to reperfuse tissue that is hypoperfused but still viable (penumbra). While there are undoubtedly other variables that are important, the overwhelming burden of animal and human data have shown that time is critical for the existence of penumbra; penumbral tissue is more plentiful the earlier the patient is treated after the stroke onset. Therefore, when NINDS patients were treated on average 90 minutes after stroke onset, the core of already infarcted tissue, represented by areas of EIC on CT, was in most cases likely still surrounded by substantial salvageable, normally appearing penumbral brain tissue on CT. Such patients could, and did, benefit from reperfusion after intravenous tPA. However, 240 to 300 minutes after the stroke, when the average ECASS patient was treated, the core would be larger (hence more patients with EIC in $>\frac{1}{3}$ MCA), and the regions of EIC would most likely be surrounded by relatively less penumbra. The result of treating such patients, therefore, is risk with less likelihood of much benefit. This logically would explain why EIC by themselves, whatever their extent, did not predict lack of benefit from tPA treatment in the NINDS patients, but why extensive EIC were associated with risk and no benefit in ECASS.

This hypothesis is supported by clinical observation of patients seen within 3 hours of stroke onset in the middle cerebral artery territory in whom it is not uncommon to see EIC. In most of these patients with EIC, their clinical deficit is severe, with high NIHSS scores, representing dysfunction in more extensively involved hypoperfused penumbral tissue than would be expected from injury to just the areas of insular cortex, putamen, and capsular hypointensities that comprise their EIC. Analogous to the theory (still unproven) regarding the importance of PWI/DWI “mismatch” based on MRI studies, I hypothesize that patients with such “NIHSS/EIC mismatch” might benefit from intravenous tPA more than for patients without such NIHSS/EIC mismatch, i.e., with lower NIHSS scores that match EIC in $<\frac{1}{3}$ of the MCA territory, or high scores and extensive EIC in most of the MCA territory. This hypothesis could be easily tested by re-review of the NINDS study database.

In summary, at least within 3 hours of symptom onset, the data indicate that the extent of EIC is not critical to decision-making regarding the use of tPA. It is more likely that whether there is continued existence of hypoperfused penumbral tissue is what is important. Based on the above reasoning, the differences between the NINDS and ECASS data on this issue make complete sense and should not foster confusion, further “controversy,” or excuse not to treat. For patients who meet published criteria and can be treated within 3 hours of symptom onset, until further data are forthcoming testing the validity of the mismatch theory (either MRI PWI/DWI mismatch or clinical NIHSS/EIC mismatch), the conclusion of the NINDS group should be followed and such patients should be treated even in the presence of EIC.

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1. von Kummer R. Early major ischemic changes on computed tomography should preclude the use of tissue plasminogen activator. Stroke. 2003;34: 820–821.

2. Lyden P. Early major ischemic changes on computed tomography should not preclude the use of tissue plasminogen activator. Stroke. 2003;34: 821–822.


Response

Dr Grotta’s kind suggestion to overcome a discrepancy between the NINDS and ECASS investigators deserves a thoughtful response. He hypothesizes that “early ischemic changes (EIC)”4 on CT, whatever their extent, do not affect the benefit from tPA treatment if this treatment is initiated within the first 3 hours (like in the NINDS patients), but may be associated with risk and no benefit if extended and the treatment is delayed beyond 3 hours (like in most of the ECASS patients). His alternative view suggests that the core of ischemic infarcts is continuously growing at the expense of the penumbra in all patients with ischemic stroke. If we define EIC as hypoattenuating brain tissue due to water uptake in brain regions suffering from severe ischemia and presenting the core of the infarct and irreversible injury,1 extension of EIC, eg, covering the entire MCA territory, has a penumbra zone for the first 3 hours that is worthy of rescue by reperfusion.

Although I appreciate very much each attempt to elucidate the arguments and to overcome this controversy,2,3 I do not see the evidence supporting this hypothesis. Zülch, a German neuropathologist, carefully studied the patterns of ischemic brain infarcts and showed years ago that the occlusion of the MCA trunk could cause small or extended infarcts depending on the capacity of collateral vessels and perfusion pressure.4 Under adverse conditions, the entire territory of an occluded brain artery is lost within minutes. The immediate loss of brain tissue can be small, if the occlusion is more distal within the arterial tree. On CT, small or large ischemic edema is present in about two thirds of patients within the first 3 hours and does not change very much over time regarding its extent.3 A continuous concentric growth into the surrounding penumbra as suggested by drawings on scientific slides does not reflect reality. The infarct growth in unfortunate patients is better explained by the stepwise recruitment of other arterial territories that cannot provide sufficient blood flow for the brain to survive. Thrombolysis even within 3 hours cannot revitalize this tissue. Increased blood flow through damaged tissue may mean a risk for edema and hemorrhage.

Fortunately, in the majority of stroke patients, collateral blood flow keeps major portions of the arterial territory vital and enables the recovery of neuronal function after recanalization and reperfusion. These patients present with normal CT or with only a limited extent of ischemic damage in contrast to a proximal location of arterial occlusion and their poor neurological scores. The typical patient in this group has a high NIHSS caused by MCA trunk occlusion, but hypoattenuation of the basal ganglia only. Here we find the mismatch between a high NIHSS and relatively small volume of hypotenuating brain tissue. Successful thrombolysis in these patients will rescue the entire MCA territory with the exception of the basal ganglia. The chance for this benefit is better the earlier the treatment is initiated for obvious reasons. So far, we have no controversy. There are, however, also patients with extended hypoattenuating brain tissue within the first 3 hours that match the high NIHSS. Dr Grotta states that such patients may benefit less from tPA treatment than patients with a similar clinical score, but only a small volume of hypotenuating tissue. I agree, and that is why the extent of hypoattenuating brain tissue in acute stroke patients really matters.

The NINDS trials and other experiences have shown that the extent of ischemic damage really has an impact on treatment response regardless of whether the patient is treated within or beyond 3 hours. In a secondary analysis, the NINDS investigators detected 84 patients (14%) with EIC exceeding one third of the MCA territory.3 This number was only 52 patients (8%) in ECASS-1 and 37 patients (5%) in ECASS-2. In the NINDS trials, mortality in these patients was 34% in the treated group compared with 18% in patients with EIC $<\frac{1}{3}$ MCA territory and 14% in patients without EIC. The unadjusted OR for death at 90 days was 2.2 (95% CI, 1.0 to 4.7).
compared with the placebo-treated patients without EIC. The adjusted OR was 1.2 (0.5 to 2.9), whereas the tPA-treated patients without EIC or with \(<\frac{1}{3}\) MCA territory EIC showed a trend for reduced mortality (OR: 0.7, 0.4 to 1.3). It is clear that the prevalence of EIC in the NINDS trial is far too small to really study the clinical significance of EIC and to avoid a type II error. I am not in favor, however, of missing the trend of these data and of concluding that EIC are clinically insignificant, because we have other observations beside the ECASS pointing in the same direction. Barber et al scored prospectively the baseline CT of 156 patients treated with tPA within 3 hours. They found 65 patients (42%) with an ASPECTS of \(<8\). That means that these patients had EIC in \(>2\) out of 10 indicated brain regions, which describes a similar cut-off as the \(\frac{1}{3}\) MCA rule. Despite early treatment with tPA, these patients had a poor outcome with dependency and death in 62 patients (95%) and symptomatic hemorrhage in 9 patients (14%). Dependency and death occurred in only 20% of patients with less extended EIC, and only 1 patient (1%) of this group had a symptomatic hemorrhage. I would, therefore, not recommend treating patients with tPA within the first 3 hours if their ASPECTS is \(<8\) or the volume of their hypoattenuating brain tissue is \(>\frac{1}{3}\) of the MCA territory, until a benefit from tPA is proved for these patients.

Some of this controversy could be avoided if we would use common terms and definitions in describing CT findings in stroke patients. “Early ischemic changes” and “signs” do not describe what pathology is meant; and the term “symptomatic hemorrhage” is widely misused. In my view, the uptake of water by ischemic brain tissue that causes a decrease in x-ray attenuation is the key finding of CT because it identifies irreversible tissue injury with high specificity. Hypoattenuation is each visible loss in x-ray attenuation. In our experience, even a “subtle” decrease in x-ray attenuation heralds tissue necrosis under ischemic conditions. Where is the evidence that subtlety means reversibility, as is suggested by Dr Lyden? The term “hypodensity” is ambiguous if a measure for “density” is not provided. Other terms such as “loss of gray/white matter distinction,” “loss of the insular ribbon,” and “obscuration of the lentiform nucleus” just describe the consequences of hypoattenuating brain structures. Without a clear concept and language of the stroke pathology being detected by CT or MRI, important findings will further be missed and their relevance for patient management will be underestimated and remain a matter of debate.

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Response
We thank Dr Grotta for his comments on the Controversies in Stroke editorial concerning the significance of early ischemic changes (EIC) on CT after acute stroke and the implications for thrombolytic therapy.

We agree that the frequency and extent of penumbral tissue is time-linked and this finding correlates with the reducing efficacy of tPA over the 3-hour time window. Similarly, EIC become more common over time from stroke onset and this certainly helps to explain the difference in the perspective of the American and European tPA investigators. Dr Grotta’s suggestion that patients with “NIHSS/EIC mismatch” (neurological impairment out of proportion to EIC) might predict tPA response is very much in line with the suggestion of other investigators, who have similarly hypothesized that “clinical-DWI mismatch” on MRI also predicts the presence of a substantial penumbra and the potential for treatment benefit. This issue certainly warrants further study.

Whether or not sub-3-hour tPA candidates should be excluded on the basis of substantial EIC remains unresolved in our view. However, we continue to urge caution in this setting, in line with published guidelines concerning use of thrombolytic therapy in acute stroke.4

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