Recanalization and Stroke Outcome

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Since work in the early 1980s suggested that acute recanalization of an occluded brain-supplying artery was feasible, a series of small uncontrolled and controlled studies supported the notion that recanalization could improve the outcome of ischemic stroke.¹ That early work paralleled similar successful efforts to achieve recanalization of occluded coronary arteries with plasminogen activators in patients presenting acutely with myocardial ischemia. The very nature of the outcomes of ischemic cerebrovascular disease, that demise does not reflect the evolution of brain injury, different from myocardial ischemia, has required rapid, readily applicable reproducible assessments that include neurological deficits and types and grades of disability. These reflect the arterial supply of the brain and its regional specialization of function: motor skills, sensory perception, speech, association areas (mostly silent), cognition, automatic function, and countless others. This complexity of functions vulnerable to focal ischemia, the variations in arterial supply from patient to patient, and differences in occlusion location within a single brain-supplying artery ensure that outcomes can be quite heterogeneous. From the outset, it has been recognized that instruments for outcome measures must capture these variables. To date, the most versatile instruments reflect functions that can be readily detected by the neurological examination. But, obtaining information regarding arterial supply and occlusion location together in the acute setting requires formal imaging techniques. This information cannot be exactly deduced by the neurological examination alone.

Recanalization of Cerebral Arteries Improves Outcome

The hypothesis that recanalization of an occluding thrombus in the symptom-producing cerebral artery could improve neurological function (reduce disability) became testable when the fibrinolytic approach was applied early enough to allow restoration of flow but not substantially increase the risk of hemorrhagic transformation.²³ Mori et al⁴ and Yamaguchi et al⁵ both demonstrated a relationship between acute recanalization documented by cerebral angiography and neurological outcome. In those studies, outcome was measured with rather simple outcome instruments based on the neurological examination. Both prospective randomized trials indicated that recanalization in the presence of 2-chain recombinant tissue-type plasminogen activator (rt-PA; dute-plase) was superior to placebo without excess risk of intracerebral hemorrhage and that neurological outcome was improved. A parallel dose-finding experiment with 2-chain rt-PA demonstrated that obstructions more distal in the middle cerebral artery territory were more likely to undergo recanalization than those more proximal (internal carotid artery).³ In addition, that study prospectively acquired serial data on each patient before and after thrombolysis based on the neurological examination and collected on the template of the Harvard Cooperative Stroke Registry.⁵⁶ Neurological status could then be related to recanalization in a post hoc fashion. Importantly, the registry used a data collection instrument that was descriptive and therefore not ordinal and not subject to a weighting bias.

The use of clinical assessment scales for stroke outcome is one of the very interesting issues raised by the article by Mikulik and colleagues in this issue of Circulation.⁷ Data from the Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic t-PA (CLOTBUST) trial were reexamined to compare outcome according to the National Institutes of Neurological Disorders and Stroke (NIHSS) stroke scale, an ordinal scale, with apparent recanalization by transcranial Doppler (TCD) ultrasonography. Data from the phase I feasibility study (of transmitted ultrasound thrombus disruption with systemic rt-PA) and the phase II CLOTBUST trial have been reported previously in several forms.⁸⁹ This post hoc analysis suggests that a relationship exists between NIHSS score and TCD evidence of recanalization and that this relationship can be optimized by seeking a threshold score change that reflects improvement. Perhaps the most important aspect of this data analysis is the attempt to quantify a relationship between recanalization of a cerebral artery and its impact on neurological function. There are several premises inherent in this analysis: (1) the relationship between TCD and angiography in detecting both patent and occluded cerebral arteries, (2) assessment of recanalization in the acute setting, (3) the relationship of ordinal scales to the observed deficits, and (4) the effective sensitivity of such scales to change in neurological outcome.

Cerebral Angiography and TCD in the Acute Setting

Contrast angiography and magnetic resonance angiography can define the status of occlusions of the proximal middle cerebral artery and other intracerebral arteries and are taken...
as the standard. Several limited studies have compared the ability of TCD in experienced hands with angiography in the same patient to exactly reflect the occlusion status of a proximal cerebral artery. In the late 1980s, the La Sapienza group in Rome demonstrated high correlations between evidence of occlusion determined by TCD and angiography.10–12 That experience has been extended more recently with newer technologies.13,14 TCD evaluation of both internal carotid artery and middle cerebral artery occlusions confirmed the report of del Zoppo et al, demonstrating a gradient of increased frequency of recanalization of more distal cerebral arteries acutely in stroke patients.3,15 A very high sensitivity and specificity were observed for the use of TCD compared with digital subtraction magnetic resonance angiography when performed late (mean, 12 and 41 hours after stroke onset, respectively)16 or early (mean, ≈90 and 174 minutes after stroke onset, respectively) after stroke.17 The ability of TCD to reliably detect acutely occluded cerebral arteries is only now being studied consistently. Recently, suggested “practice standards” have provided insonation depths for individual cerebral arteries and their anticipated waveforms, but use acutely in stroke is not yet addressed.18

The limitations of TCD in this setting are the requirement for a proper bone window in a nonagitated patient and experience. There is still insufficient experience with these procedures in stroke in the broader context beyond centers with real capability, which makes use of TCD in proper hands to define the occlusion status of a proximal artery segment in acceptable patients suffering an ischemic stroke forewarning but not the standard.

### Outcome Scales in Stroke

The NIHSS scoring instrument, which was the basis for the post hoc comparison of recanalization with outcome from the CLOTBUST database, differs from a data collection device such as the Harvard Stroke Registry in that the individual elements (eg, motor strength of the upper arm) are weighted in a simple but arbitrary way in the NIHSS. The need for such a tool grew in part out of the requirement to describe outcome in terms of what clinicians understand most readily, the physical examination. Other stroke scale scores, developed independently, such as the Scandinavian Stroke Scale, the Canadian Neurological Score, and others have similar features. Reassuringly, while not easily interchangeable, they are very well correlated,19 which is not surprising because they each derive from the neurological examination.

Another feature of the NIHSS is its specific limitation to the anterior or carotid artery circulation. Injury to brain stem functions from occlusions of the vertebral-basilar artery system are not readily captured by this scale. The bigger issue is how to handle the composite score represented by the NIHSS and similar scoring instruments. We describe our patients in terms of their deficits, but studies require a summary description or score. Among the useful observations with the summary score is how different stroke subtypes behave. Wityk et al20 studied 50 ischemic stroke patients treated with conventional therapy and found that the NIHSS scores of patients with lacunar infarcts did not significantly improve by day 10, in contrast to patients with middle cerebral artery territory emboli. Furthermore, the baseline NIHSS score indicates ultimate outcome (in the absence of reperfusion).21 In the setting of rt-PA exposure, the best outcomes occurred in patients with baseline NIHSS scores of 10 to 14 compared with placebo treatment.22 Curiously, among 3 prospective, controlled, and blinded trials of rt-PA treatment in acute ischemic stroke patients, before 3 or 6 hours from symptom onset, outcome was quite different despite nearly identical baseline NIHSS scores (median, 13 to 14).22–24 The reasons have not been easy to figure out but suggest that there are important subtleties in the evolving cerebral injury that are not captured by the NIHSS composite score. Again, clinical scales are typically ordinal, not numerical, which argues against the presentation and interpretation of scales on a strict numerical basis as in the Mikulik et al study.25

So, is it possible that some component of the NIHSS examination, or the neurological examination in general, could be a more sensitive indicator of outcome?

### Back to the Future

Operationally, the NIHSS score represents a reduction of all the data elements to a single score. There are benefits accruing from the use of a summary score, including clinical validity (so long as the individual components comprising the score are each clinically important disease manifestations that have face validity), avoidance of multiplicity, and improved sensitivity as a result of an expected reduction in measurement noise. Nevertheless, the fundamental question is whether the reduction of information from a large number of elements to an overall single quantity or score provides an adequate representation of the information available in the original clinical assessments. In particular, it is not at all obvious how to determine the optimal weights or, more generally, what constitutes the best method of combining the individual measures into a single index. One way to determine the appropriate set of weights is to use the principal components analysis.26 An important initial step in this process is to examine the individual components or elements to ensure their reproducibility and validity.27

The basic principles, methods, and terminology used to evaluate scales for clinical research are well established. In addition, the use of composite scores for neurological assessment is pervasive. For example, in multiple sclerosis, one rating method converted the neurological examination into a weighted ordinal impairment scale.28 The various items making up the impairment scale were not expected to be homogeneous, so it was not at all surprising that various components of the scale appeared more responsive than the overall summary measure and others appeared less responsive to a treatment.29 So, one could postulate that in the stroke study reported by Mikulik and colleagues, certain components of the neurological examination might well be more sensitive to arterial recanalization than the summary NIHSS score and that other components are less sensitive.

This appears to be the case. In the prospective 2-chain rt-PA dose-finding study, 93 (of 104) patients with symptomatic documented cerebral arterial occlusions completed the intravenous rt-PA infusion within 5.4±1.7 hours after symp-
tom onset. Each patient was scored by the same neurologist at baseline; 24, 48, and 72 hours; and subsequently, according to the unweighted neurological examination based on the Harvard Stroke Registry. After rt-PA infusion, 4 patients achieved complete recanalization, 31 had partial recanalization, and 58 experienced no recanalization by angiography at the completion of the rt-PA infusion.

The neurological examination was divided into 4 subcategories: (1) general characteristics, including neurological status, consciousness, behavior, visual fields, eye movements, weakness, and sensory; (2) behavioral examination, consisting of hemineglect, language, nondominant syndrome, and memory disturbance; (3) sensory examination, consisting of face, shoulder, hand, hip, foot, and trunk evaluations; and (4) motor examination, consisting of tongue, face, shoulder, hand, hip, and foot evaluations. We found no significant difference between the complete/partial recanalization (35 patients) and no recanalization (58 patients) groups for each of the categories, with the exception of the sensory examination. To examine this difference further, the proportions of patients with abnormal findings for the hand and face sensation components of the sensory examination at each time point were observed (the Figure). Patients who achieved complete or partial recanalization improved dramatically over the first 24 hours compared with those patients without recanalization. Thereafter, the sensory responses seemed stable within each group. In that particular trial, then, sensation seemed to be an early (24 hour) indicator of recanalization status, more so than the other components of the neurological examination. Such fine distinctions may well be obscured in a summary measure, particularly if little weight is accorded the sensation domain in the summary. It is clear that, in that trial, severity of stroke at baseline as judged by neurological examination was related to recanalization outcome.

Summary

All of these considerations draw attention to the utility of summary stroke scale scores in assessing cerebral artery occlusion status acutely, a topic explored nearly 20 years ago. Is the use of TCD in this exercise minestrone riscaldai?


**KEY WORDS:** Editorials ■ angiography ■ cerebrovascular circulation ■ reperfusion ■ stroke ■ ultrasonics
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Circulation. 2007;115:2602-2605
doi: 10.1161/CIRCULATIONAHA.107.698225
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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