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Acute ischemic stroke is a heterogeneous disease process that defies simple definition. It might be likened to a Greek drama, too frequently a tragedy, wherein the dramatis personae (the nature and etiology of the arterial occlusive lesion [AOL], the duration of the ischemia, the nature of the neurologic deficit, the therapy, the time to therapy (TTT), the time to recanalization, the available collateral blood flow, the cellular bases for metabolic alterations in the ischemic end organ, and other patient-specific comorbid factors) all interact to determine the final act. Uncertainty about the ending is punctuated by skepticism that external forces (the therapy) will actually alter the denouement.

Evidence that the course can be altered or reversed in some patients is compelling, however. Scientific evidence, produced in two consecutive, appropriately designed studies (as required for Food and Drug Administration [FDA] approval) has shown that IV infusion of recombinant tissue plasminogen activator (rTPA, or alteplase), given within 3 hours of onset, leads to 31% better outcomes in treated patients as opposed to untreated control subjects (1). This benefit extends across all levels of neurologic deficit and presumed stroke type, despite a tenfold increase in symptomatic intracerebral hemorrhage in treated patients. Approximately 20% of patients died with (17%) or without (21%) treatment. These results have been substantiated in subsequent multicenter analysis as well (2).

IV rTPA opens AOLs; however, it does not open all AOLs equally. Larger vessels, such as the internal carotid artery (ICA) or the M1 segment of the middle cerebral artery (MCA), have a presumably greater thrombus burden, a poorer supply of the lytic agent to the AOL, and apparently open less frequently than the more distal M2 divisions and M3 and M4 cortical branches (3). IV rTPA also improves patient outcome; however, it does not benefit all patients equally. The nature of the initial neurologic deficit as measured by the National Institutes of Health Stroke Scale Score (NIHSSS) predicts the outcome to some degree. Fifty-two percent of treated patients with NIHSSS < 10 will achieve improvement to NIHSS 0 to 1, but only 8% of patients with NIHSSS > 20 will do so (4) The odds ratio of improving to NIHSSS $= 0$ or 1 with treatment is approximately 1.6 for NIHSSS $<$ 10, but approximately 6 for NIHSSS > 20.

The nature of the AOL in major acute ischemic stroke is quite heterogeneous, but well known. When examined by angiography within 6 hours of acute onset, approximately 30% of patients will have an M1 occlusion, 25% will have an M2 occlusion, 10% will have a carotid ''T'' occlusion, 15–20% will have a proximal ICA occlusion or severe stenosis (typically with distal thromboembolism), 5–10% will have a vertebrobasilar occlusion, and 10–20% may exhibit no major AOL (possibly because of intercurrent recanalization) (5–7). Is there some recanalization treatment for AOLs available for patients who cannot be treated with IV TPA within 3 hours, particularly those patients with greater deficit and larger vessel occlusion that does not typically respond well to IV TPA? The answer is yes, and no.

Direct intraarterial thrombolysis has been applied to AOLs for years. Beneficial off-label use of urokinase or rTPA has been reported in a number of uncontrolled, nonrandomized case series, and many neurointerventionists have adopted this therapy, making it standard practice in many communities. Theoretically, all major AOLs may be treated with intraarterial thrombolysis. A number of nonrandomized treatment series have indicated that the natural history of acute basilar artery occlusion (75% major disability or death) may be dramatically altered with intraarterial thrombolysis of the basilar artery (8–10). Prolyse in Acute Cerebral Thromboembolism Trial (PROACT) II represented the first randomized, controlled analysis of intraarterial thrombolysis in a homogeneous group of AOLs (M1 or M2 occlusions) in patients with major neurologic deficit (median NIHSSS = 18). The study clearly revealed the poor natural history of medically treated M1 or M2 occlusion, verifying previous reports. In the control group treated with IV heparin (n = 59), at 3 months 48% were disabled, 25% were independent (modified Rankin Score 0–2), and approximately 25% had died.

PROACT II revealed the usefulness of local intraarterial fibrinolysis in achieving better outcomes. Patients treated with 9 mg of prourokinase (n = 121) did 60% better than control patients (40% vs 25% achieved a mean Rankin Score of 0–2, $P = .047$, at 3 months). This benefit was achieved despite an increased symptomatic hemorrhage risk in treated patients (10% vs 2%). Approximately 25% of patients in PROACT II died, indicating that mortality may not be altered by anything but the most timely and effective treatment. Of note is that approximately 20% of patients died in the National Institute of Neurological Disorders and Stroke

(NINDS) study, in treated and control groups, as well.

The results of PROACT II, although scientifically positive, did not satisfy the regulatory requirements for drug approval that call for one overwhelmingly positive study or two studies sufficiently positive as to prove efficacy. Nevertheless, it did establish ''proof of principle'' that intraarterial thrombolysis is an effective therapy, even when administered late in the ischemic process (PROACT median TTT = 5.3 hr).

With the failure of prourokinase to achieve FDA approval for the treatment of intraarterial thrombolysis for stroke, and the withdrawal of urokinase from the market as a drug to treat pulmonary embolism, few options appeared to remain. This situation prompted the FDA to make a statement concerning alternative available pharmaceutical agents, including rTPA (Activase) and streptokinase (Streptase). Only one small, randomized controlled study of intraarterial rTPA use for emergency stroke intervention has been reported. The Emergency Management of Stroke (EMS) study treated patients randomly with IV TPA or placebo, followed by an angiogram, then intraarterial thrombolysis (20 mg TPA up to 2 hours) if an AOL was revealed (11). Fifteen patients had M1 or M2 occlusions, six in the placebo group and nine in the TPA group. Ten of the 15 patients achieved mean Rankin Scores of 0–2 at 3 months (66%); five (55%) were in the combined therapy group and five (83%) were in the intraarterial-only group. Mean intraarterial TTT was 4.2 hours. Although it appears that the combined treatment is responsible for the good outcomes, it may actually be the early TTT that is responsible for the overwhelmingly positive results suggested in this small trial. Subsequent application of a similar treatment paradigm, where intraarterial TTT was reduced to 3.3 hours, led to similar results (R. Ernst, personal communication).

No trial reports for stroke therapy are yet available for IV or intraarterial reteplase (rPA), a deletion hybrid tissue plasminogen activator with slightly different physicochemical characteristics. Anecdotal reports of low-dose intraarterial stroke therapy with rPA are encouraging, however. Antiplatelet agents, such as IIb/IIIa inhibitors, may promote clot dissolution by altering interplatelet bonds and preventing interplatelet adhesiveness. A single randomized trial of 70 patients, randomized 2:1 to active drug, suggests safety with TTT up to 24 hours, with some suggestion of potential efficacy (12).

PROACT II provided ''proof of principle'' that intraarterial thrombolysis works for some patients and can improve the natural history of severe stroke in a time window that may represent a worst-case scenario. The 5.3-hour TTT can be improved in clinical practice where delays inherent in a study are obviated. Other recently published intraarterial case series echoes the EMS results that timing is important. Suarez et al reported 56% good outcomes for therapy of MCA occlusion with mean TTT of 4.6 hours (13). Bendzus et al reported 66% good outcomes in 12 patients with treatment begun within 4 hours (14). Better outcomes were associated with earlier treatment in the NINDS trial, as well as in patients treated as standard of care post-NINDS (15, 16). If 40–66% good outcomes with MCA occlusion may be offered to patients with timely treatment, how can that opportunity not be offered to a patient faced with only 25% likelihood of good outcome if no intervention is instituted?

Better patient selection might allow us to choose the patients most likely to improve with treatment, and reject those that are unlikely to be helped, or even likely to be injured. First, how can we effectively screen stroke patients for those likely to have a major AOL? Simple noncontrast CT is a useful preliminary test in finding treatment candidates. The AOL was revealed by the hyperdense MCA sign in 33% of the randomized PROACT II patients. This approximates the incidence in other major stroke studies and reminds us that many major stroke patients do not need additional, noninvasive, vascular imaging merely to confirm an AOL.

In the remaining patients, CT angiography of the circle of Willis immediately following the noncontrast CT has been shown to have a high specificity for AOL (17). It is relatively quickly performed, with nearly immediate display of axial source images that do not need postprocessing for basic analysis and decision making. Perfusion CT of a brain area or volume above the circle of Willis may be performed to gain a sense of the volume of brain at risk. False-positive examinations of approximately 10% have been reported, however (18, 19), and injection/study failures are known to occur.

A xenon-CT cerebral blood flow measurement performed in the same CT scanner can show the level of AOL, the volume of brain at risk based on reduced cerebral blood flow, and may estimate the risks of reperfusion hemorrhage from thrombolytic therapy. Nonetheless, performance and processing take 20–30 minutes, and it remains to be seen how many genuine thrombolytic candidates are excluded from therapy with this form of evaluation (20–22). A single-photon emission CT radioisotope study was reported to show the volume of brain at risk and also predict the risks of reperfusion hemorrhage (23).

MR arteriography can show that an AOL is present, but does not always clearly define the exact level and extent of the occlusion, particularly in cases of ICA occlusion and distal embolus. Its high sensitivity for identification of major AOLs, however, is its chief recommendation; it easily excludes those not in need of recanalization efforts.

MR arteriography can be combined with diffusion- and perfusion-weighted imaging. Diffusion-weighted imaging reveals the volume of brain suffering loss of normal water movement, and perfusion-weighted imaging shows the volume of brain at risk for ongoing damage as the ischemia persists (24). When the volume at risk approxi-

mates the volume already damaged, a ''matched'' condition exists. In this patient population, thrombolysis may have little benefit and may subject the patient to the risk of, or even promote, intracerebral hemorrhage. When the volume at risk is larger than the volume already damaged, a ''mismatch'' exists. Theoretically, this is the patient population that would benefit most from thrombolytic therapy. Scant substantive data are available, however, on the likelihood of matches or mismatches at varying time points in genuine treatment candidates. Studies to date suggest that 20% of major stroke patients will exhibit a matched defect, whereas 80% will have a mismatch in the first 6 hours (25–27). Those who fail to recanalize have larger infarcts (25). Is it worth the time, effort, and money to try to exclude 20% of patients? Viewed from a different perspective, is there greater harm in delaying therapy for 80% of the patients by trying to eliminate the 20% who may not be helped?

Could the ideal diagnostic algorithm actually be a combination of the above tests, according to different clinical circumstances, to select appropriate treatment candidates? Are there other data that might indicate a better primary triage point for further evaluation and treatment? Consider for a moment a hypothetical test that can be done in any ambulance on the way to the emergency room; it is reproducible, requires little hardware and is inexpensive, does not require postprocessing, does not delay treatment 20 or 30 minutes, and can identify the patients that have a high likelihood of major AOL. ''Where can I buy it?'' everyone asks. It is the physical examination and determination of the NIHSSS.

Whereas the NIHSSS does emphasize left hemisphere AOLs because of increased points related to speech function, it is a very useful predictor of an AOL (28). In patients presenting with carotid distribution signs, low stroke scale score (< 9) is unlikely because of an AOL large enough to necessitate thrombolytic therapy. The NINDS pilot trial first showed that the hyperdense MCA sign (as a marker of MCA occlusion) was associated with NIHSSS > 10 (29). Only 13% of M1 or M2 occlusions in PROACT II had NIHSSS < 10, and such patients who were treated did no better than untreated control subjects, on average. EMS suggested that 100% of patients with NIHSSS > 14 had a major AOL. How much greater specificity in predicting the presence of a major AOL is needed to act? CT angiography has a 10% failure/false-negative rate. MR with diffusion- and perfusion-weighted imaging may have an equal failure rate caused by lack of patient cooperation, and may exclude only 20% of patients from treatment, delaying treatment for the rest.

If TTT is important, as is almost certainly the case, interesting sensitivity analyses may be constructed, taking into account the delay in TTT inherent in a test, the percentage of patients the test excludes from further evaluation/treatment, the time after stroke onset, and possibly the severity of the neurologic deficit/NIHSSS. For example, perhaps a patient with NIHSSS of 20, with only a 15–20% chance of a diffusion-/perfusion-weighted imaging match at 2 hours into the ischemic episode, should be taken directly into the angiography suite for thrombolysis, whereas at 5–6 hours postictus, the chance of a match might increase to 40% or 50%, and it may be reasonable to delay 20–30 minutes before performing the test.

The foregoing discussions do not even touch on the impact of future advances in recanalization. The time to recanalization is part of the ischemic duration that is factored into the time discussion with great difficulty. Thrombolysis recanalizes approximately 70–80% of MCA occlusions within 2 hours. What if a device reduces the recanalization time to 1 hour, or even to 10 minutes? Then we will have to think in terms of time to recanalization rather than TTT, and our sensitivity analysis curves will have to be adjusted appropriately. This one factor can have extreme implications, perhaps opening the window of therapy even wider.

The preceding paragraphs emphasize that there is much to learn about appropriate patient selection. How does this lack of perfect scientific information, which may only be resolved with years of research effort, affect our current management of a disease process that probably has less than 50 000 legitimate thrombolysis-treatment candidates yearly across the United States? How might we more consistently improve outcomes from the low natural history expectation of 25% good outcome up to 50% or greater?

Hypocrites' admonition is perhaps tested no more directly than in intraarterial thrombolysis. Some patients will be harmed by intracerebral bleeding who might otherwise have survived with limited disability. Some patients will survive with disability that might otherwise have died. But available evidence suggests that, in general, disability-free survival may be offered to up to twice as many patients. Presenting these realities and choices to the family of a loved one faced with the prospect of life-long disability (or perhaps death) should meet the obligations of informed consent.

In the absence of a drug specifically labeled for intraarterial thrombolysis for stroke on the basis of regulatory approval, what is a responsible physician to do? The relatively low occurrence rate of this heterogeneous disease process in any one center does not easily lend itself to analysis. For PROACT II, over 10 000 patients were screened to find 480 patients eligible for angiography, of which only 180 patients with M1 or M2 occlusion were found that could be randomized for the study. The reluctance of drug companies to fund expensive studies with relatively low projected use of the agent even if approved, just to create improved scientific certainty, is understandable. To obtain funding from government sources to begin additional stroke treatment studies may take years. All the information available regarding thrombolytic therapy tells us that to delay treatment 15 or 30 minutes

diminishes good outcomes. Delaying years certainly must do the same. We must act on the data currently available to us, and review other data that become available.

The American Society of Interventional and Therapeutic Neuroradiology (ASITN) believes that treating a suitable patient under appropriate clinical circumstances by means of intraarterial thrombolysis is a responsible medical decision even in the absence of strict scientific guidelines. To share this opinion with the medical community, the ASITN has created a statement regarding intraarterial thrombolysis for emergency treatment of stroke. The opinion does not reflect the rosy-colored dawning of a new day, but the conviction that the ongoing 20-year odyssey has indeed produced an applicable therapy. The ASITN feels that the interventional team must take into account all available data regarding the disease process and the individual patient, and apply them in a responsible fashion according to their best judgment in order to recommend treating, or not treating, a patient with the best interventional techniques and drugs available. Like Icarus, we are flying with wings that may not be perfect. Yet, we will be successful more often than not if we are careful not to fly too high. The ASITN recognizes that its statement may be viewed by some as a Pandora's box, opening the door of interventional stroke therapy to individuals with insufficient training and experience, and possibly inviting catastrophe. Nonetheless, to weigh the available evidence and not have an opinion would be abrogating our responsibility to our patients. The statement is offered with confidence and expectation that the neurointerventional team will apply the knowledge that comes from stroke patient management, neuroimaging in arterial occlusive disease, and neurointerventional experience, in order to optimize the outcome for each individual patient as best as currently possible.

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