Why Model Strokes?

Gaetano F. Molinari, MD

In this issue of Stroke, Professor László Molnár and coworkers describe another experimental model of stroke. An apparently reversible form of embolic intravascular occlusion may now be added to previous tabulations of various methods and outcomes. Professor Molnár and coworkers have previously validated their model by light microscopic criteria to show morphologic resemblance to ischemic pathology in humans. In their current report, Molnár et al use multiple pathophysiologic monitors to show ischemic changes and their reversibility before development of permanent damage.

What is the significance, clinical relevance, and therapeutic implications of yet another published method for producing strokes in animals in this era of aggressive animal rights activism when we have transmitted (computed tomography [CT]) and emitted (positron emission tomography [PET] and single-photon emission computed tomography [SPECT]) radiation scans and nuclear magnetic resonance imaging (MRI) of the brain capable of deriving morphologic, physiologic, and even metabolic data directly from patients?

There are several advantages to the use of animal models. Most of our knowledge to date about the minute-to-minute pathogenesis of cerebral ischemia and infarction is based on detailed studies in animal models. The use of standardized animals selected for uniformity removes the uncontrollable variables encountered in human disease and permits relatively simple analysis and assessment of cause-effect relations between ischemia and infarction, pathogenesis and treatment. Certain models permit quantitative gradation of both severity and duration of the ischemic insult with infarct size in pathologic specimens both with and without specific treatment variables.

Despite the absence of a clinically proven efficacious treatment for acute strokes in humans, many therapies including barbiturates, naloxone, calcium channel blockers, and even extracranial-intracranial bypass surgery have proven effective in reducing lesion size in animal models compared with untreated controls. New therapeutic approaches that may develop into testable hypotheses in humans are suggested by the methods used to induce and reverse focal ischemia in animals. Although animal models do not lend themselves well to clinical outcome measures, the option of elective euthanasia at preselected times permits quantitative as well as qualitative pathologic assessment of the "harvested" specimen.

Offsetting these advantages, however, are considerations that complicate clinical research in human disease. Because strokes in humans are not usually fatal, the lesion itself remains inaccessible to direct observation except possibly in the few severe fatal cases or in end stages. Therefore, elaborate neurologic, physiologic, and neuropsychological testing schemes are required to measure indirectly the "size" or impact of the disease on surviving patients.

From the menu of stroke models available or yet to be contrived, the investigator may, and indeed should, select the model specifically designed to answer the posed questions to yield data appropriate to the research at hand. Unfortunately, some conclusions reached may be specific to the animal model and not generalizable to spontaneous disease states encountered in nature. Due to the huge numbers of variables encountered in clinical research, including variations in the anatomy of the circle of Willis, the duration of ischemia, the technologies used to assess end points, interrater reliability, coexistent disease states, and patient motivation, the statistical sample must be enormous to remove chance and bias from the interpretations of therapeutic data in humans.

In summary, quantifiable pathologic outcomes are the strength of animal models, but in humans, clinicopathologic correlation has become a lost art and an unfashionable source of scientific validation and learning supplanted by large-scale prospective tests seeking statistical proofs.

As to its clinical relevance, the model of Professor Molnár and coworkers suggests that emboli might be removed retrograde from their original point of occlusion. Reperfusion thereby salvages the brain tissue exposed to risk of ischemic infarction.

Since many hospitalized patients have cerebral embolism as a complication of known heart disease or during an invasive procedure or treatment, the period from onset to diagnosis is precisely known, is of minimal duration, and is readily suited to prompt therapeutic intervention. Hospitalized patients suffering from acute embolic ischemia and
incipient infarction are therefore different from persons in whom unknown times exist between discovery or reporting, arrival of assistance, transportation to a hospital, and presentation to investigative therapists.

In strokes that occur in the hospital, if an emergency angiogram or even the procedure that triggered the focal ischemia shows downstream blocks consistent with emboli or an upstream filling defect caused by a large arterial embolus still attached to an ulcerated plaque at the sinus, should not a neurosurgeon perform an emergency embolectomy? This is particularly true if the same angiogram shows paucity of intracranial atheromata and patency of distal collateral vessels perfused retrograde. Could not recently embolized downstream clots, not yet pathologically organized and stuck to blocked arterial walls, be sucked backward safely, without risk of reperfusion injury, if the duration of ischemia is less than the critical tolerance times of astrocytic glia and endothelial cells? Isn’t this the way many controversial treatments for stroke started? If experiments in several laboratories show that retrograde removal of embolic particles from the brains of several species of animals reduced lesion size or preserved neurons in the affected vascular territory compared with controls, undoubtedly there would be prompt, uncontrolled, and probably premature tests in patients, usually at the centers conducting the experiment in animal models, along with favorable reports showing “great promise” in a few individual patients. We would then be obliged to organize and launch a large-scale multicenter study using concurrent controls to achieve statistical proof of efficacy. Yet we are just as likely to be bitterly disappointed when an expensive prospective test of the therapeutic hypothesis derived from yet another animal model fails to meet statistical standards for proof in analyses of groups in large series of patients.

Perhaps we are mixing apples and oranges in this traditional investigative scenario, which uses different standards in animal studies than in human disease. We could study fewer patients better if we used strict angiographic criteria for patient selection and lesion size measured by late-stage CT scans or MRI as the basis for comparison of outcomes in treated and untreated groups. Surely the premise that in the same vascular territory a small lesion is better than a large one as a measure of outcome is not too great an act of faith to expect of even skeptical scientists as well as credulous practitioners.

The test variables become fewer in number and more objective and quantifiable in a study design using arteriography to match pairs of treated and untreated vascular lesions, according to the primary site of major occlusion and both anterograde and retrograde collateral flow patterns. Only in patients who escape with no radiologically detectable parenchymal lesion would the clinical investigator need to rely on detailed neurologic, physiologic, and neuropsychological examinations as outcome criteria. Multivariant pathophyslogic monitoring including PET scanning could be used in selected, intensively studied patient subsamples to establish normative mechanisms and timetables of both pathogenesis and recovery.

Unless we use analytic methods in the clinical tests in humans similar to those used in the animal models originally suggesting the efficacious treatment, we are destined to repeat the now familiar and recurrent sequence. Animals are sacrificed to develop protocols based on pathologic and physiologic measurements to be tested in humans using crude clinical outcomes with far poorer powers of resolution. We will probably continue to renew hope through the experimental neuropathology of animal modeling, only to be disappointed by the results of large-scale, statistically valid clinical trials that are not designed to measure comparative neuropathology in humans.

References


Key Words • animal models • cerebrovascular disorders • angiography
Why model strokes?
G F Molinari

Stroke. 1988;19:1195-1197
doi: 10.1161/01.STR.19.10.1195

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/19/10/1195.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/