Treatment of Cerebral Ischemia — Where Are We Headed

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THE PAST DECADE has witnessed an explosion of technological advances in neuroimaging and neurochemistry. Measurement of cerebral blood flow and metabolism, and radiographic and sonographic imaging of the brain and the extracranial cerebral vasculature are now far more advanced. Hematologists and experimental pathologists have begun to classify the complexities of blood coagulation and its interrelationships with atherosclerotic and other vascular lesions. We can now begin to approach the laboratory stroke model and diagnostic problems of the human stroke patient more logically and completely. Also newer stroke treatments have been developed e.g. extracranial to intracranial bypass procedures and newer "anti-platelet" drugs. These advances have given the present day clinician a more potent and complex armamentarium. With the increased complexity comes a clearer need for a strategy or a road map to plan future controlled therapeutic trials, or simply to treat the individual stroke patient in the clinic. In a prior communication, I had argued why therapeutic decisions based solely on a simple classification of patients that considered only the time course of deficit (TIA, RIND, progressing stroke, or completed stroke) were irrational and impractical. I will in this note share some thoughts on the positive side, that is, how we should be planning future treatment and trials.

There are 5 important factors that, to a large extent, determine short term and long range prognosis in patients with cerebral ischemia: 1) location and severity of the causative vascular lesion, 2) hematological state, 3) size, location and reversibility of brain ischemia, 4) intercurrent medical illness and complications of the stroke or its treatment, and 5) psycho-socio-economic factors. The latter two items which concern the general medical and social health of the patient are of course important factors in any illness and are not unique to stroke. The treating physician always must decide if serious medical illness, or non-medical socio-economic factors. The latter two items which concern the general medical and social health of the patient are of course important factors in any illness and are not unique to stroke. The treating physician always must decide if serious medical illness, or non-medical socio-economic factors. The latter two items which concern the general medical and social health of the patient are of course important factors in any illness and are not unique to stroke. The treating physician always must decide if serious medical illness, or non-medical socio-economic factors. The latter two items which concern the general medical and social health of the patient are of course important factors in any illness and are not unique to stroke. The treating physician always must decide if serious medical illness, or non-medical socio-economic factors. The latter two items which concern the general medical and social health of the patient are of course important factors in any illness and are not unique to stroke. The treating physician always must decide if serious medical illness, or non-medical socio-economic factors. The latter two items which concern the general medical and social health of the patient are of course important factors in any illness and are not unique to stroke. The treating physician always must decide if serious medical illness, or non-medical socio-economic factors. The latter two items which concern the general medical and social health of the patient are of course important factors in any illness and are not unique to stroke. The treating physician always must decide if serious medical illness, or non-medical socio-economic factors. The latter two items which concern the general medical and social health of the patient are of course important factors in any illness and are not unique to stroke. The treating physician always must decide if serious medical illness, or non-medical socio-economic factors. The latter two items which concern the general medical and social health of the patient are of course important factors in any illness and are not unique to stroke.

Ischemic stroke can be caused by lesions at various loci within the vascular bed. Using the carotid system as an example and going from proximal to distal, examples of the commonest offending vascular lesions are cardiac source emboli, carotid bifurcation plaques or stenosis, carotid siphon atherosclerosis, MCA stenosis, and lipohyalinosis of penetrating lenticulostriate branches of the MCA. Prognosis varies considerably but is different in patients with disease at each of these sites. Also important is the severity of disease. Patients with ICA origin flat plaques without ulceration or stenosis, ulcerated plaques, severe stenosis, and occlusion also vary in their natural histories and risk of further stroke. Mechanisms of ischemia also differ, the commonest being embolization with blockage of a distal vessel, and low flow with poor distal perfusion. With newer noninvasive cardiac techniques such as echocardiography and Holter monitoring, some embolicogenic lesions will be discovered. These cardiac tests are obviously not infallible since small clots or marantic endocarditis are frequently missed. Non-invasive evaluation of the nuchal carotid artery including Oculopletysmography (OPG), Doppler, and real time echo technology are now well advanced. It should now be possible to decide if the patient has severe stenosis (>95%), moderately severe stenosis (75–80%) or has either a normal extracranial vessel or less significant stenosis. Flat plaques and ulceration will not be reliably detected. Digital Subtraction Angiography (DSA) is now in common use and can accurately in most cases define severe stenosis. Arteriography, using the standard femoral or brachial arterial approach has become safer and easier especially if digital computer technology is used; in the hands of expert neuroradiologists in centers with advanced technology and a large case load, the morbidity is quite low and the informational yield high.

In considering the mechanism of stroke, the clinical picture will remain important. A sudden onset deficit developing while the patient is active is suggestive of...
embolism. Brief, short, frequent TIA's have been associated with "tight carotid stenosis." These so-called "shotgun" TIA's, venous stasis retinopathy, positional or hypotensive exacerbation of cerebral ischemia, and very low cerebral blood flow values provide evidence favoring a low flow mechanism of ischemia. A hypertensive patient with a pure motor deficit and normal noninvasive studies and CT is likely to have lipohyalinosis of penetrating vessels and a lacunar stroke.

For therapeutic trials, it should be possible to select patients whose vascular lesion is well defined e.g. cardiac emboli from mural thrombosis, internal carotid artery origin severe stenosis, middle cerebral artery stenosis etc. In approaching the patient in the clinic, it should be possible from noninvasive data to at least separate those patients with severe extracranial stenosis from the other groups.

### Blood, Serum, and Coagulation Factors

Hemoglobin, hematocrit, platelet counts and prothrombin time are routinely available in most medical centers. Polycythemia and thrombocytosis can alter blood flow and may potentiate a vascular lesion. In some centers platelet adhesiveness and agglutination can also be quantitated. Biochemical measures of platelet function e.g. platelet factor 4, beta thromboglobulin (BTG) or estimates of thromboxane (TxB2) or prostacyclin can now be made. Since these factors can play a role in ischemia, it is probably prudent to study those patients with important hematological abnormalities in a separate subgroup especially if there are no serious vascular occlusive lesions. Some other circulating serological factors such as blood sugar can also play a role in stroke and should be considered. We have recently examined 6 patients with stroke and coexistent hypercalcemia due to hyperparathyroidism, a relationship also occasionally noted by others, that make us wonder if hypercalcemia could also be a factor in some patients.

### Extent of the Brain Ischemia and its Reversibility

The nature of the clinical deficit does reflect the parts of the brain that are dysfunctional. It does not however reflect whether the tissue is temporarily and transiently injured, damaged beyond repair, or reversibly injured. The duration and change in the deficit often give helpful inferences e.g. a deficit which is fixed for 1 week is more likely to represent damage than a deficit present for hours and beginning to improve. Technology is now evolving to deliver more objective information about flow to the affected region and metabolism and viability. CT is clearly helpful but the rules for its interpretation have been poorly studied. A CT scan early in the evolution of a stroke showing a large region of hypodensity suggests serious damage whereas, in a patient with equally severe clinical signs, a negative CT may possibly indicate less permanent or severe damage. Do all brain lobes and tissues (cerebellum, brain stem, basal gray matter) image similarly on CT? Do certain types of damage e.g. emboli or low flow behave differently? What are the precise rules for the timing of appearance of CT lesions? Are the rules different at 12 and 36 hours? These questions have not been well studied but are of critical practical importance. Newer technology such as PET scanning is beginning to yield important data regarding blood flow and viability. In the normal situation blood flow (as measured by oxygen 15 or Ammonia 13) and metabolism (as measured by 18-fluoro-deoxy-glucose) are matched. The oxygen extraction fraction (OEF) is a good index of metabolic activity and can be calculated from the other parameters. In patients with an area of irreversibly damaged brain, metabolism and OEF are both usually low. Blood flow may be relatively high (luxury perfusion) but later is usually reduced because of the decreased metabolic activity. In contrast a viable region often has reduced blood flow but a high OEF and relatively preserved metabolism, a situation called "misery perfusion" syndrome by Baron and colleagues. Technology in this field is rapidly expanding and 3 other techniques: xenon flow coupled with CT imaging, single photon emission tomography (SPECT) and nuclear magnetic resonance (NMR) all promise to yield useful data but are to date only beginning to be carefully studied. PET requires a cyclotron to generate radioisotopes and its expense and long scanning time will undoubtedly make it very impractical for use in the average hospital or clinic. The other techniques should prove more manageable. Study in isolated specially equipped centers of PET results in conjunction with SPECT, CT and NMR may make it possible to translate the PET results into these more widely available studies and yield useful inferences regarding regional cerebral blood flow, OEF and CMR02 in regions of ischemic brain tissue. Though not a present reality, within the next decade there should be technology and data that will give the clinician information about brain ischemia and metabolism.

### Treatment

Armed with knowledge of the nature and location of the vascular lesion, the makeup and coagulability of the blood, and the state of the endangered brain, the alert clinician should be able to make more logical treatment decisions. Surely as a prelude to trials of therapy more data will be needed from study of natural history using certain constellations of findings. Examples might include: 1) occlusion of the internal carotid artery in a patient with normal coagulation and no clinical deficit, normal CT and reduced regional RCBF but increased OEF; 2) a nonstenosing internal carotid artery plaque with embolic occlusion of the upper trunk of the middle cerebral artery, clinical findings of severe hemiparesis, hemisensory loss and aphasia, normal blood findings, and a large region of frontal hypodensity by CT and markedly reduced RCBF and OEF in this hypodense zone; 3) a pure motor stroke in a hypertensive man with normal blood, moderately severe paresis of the left face, arm and leg, a 5 mm hypodensity on CT in the right posterior limb of the internal capsule, and
normal blood flow. Of course, clinical trials could not hope to be able to capture all or even most of these factors, but would concentrate on the most important variables. Stroke registries can be searched for complex variable relationships and could provide a nidus of basic information on which to base future trials.

There are two different strategies that might be used for therapeutic trials. The first involves identifying 2 or 3 of the most important variables and controlling for them. A second strategy identifies the single most important variable to be studied; other important variables are identified and measured and the data are later analyzed with respect to each of these variables. The variables chosen will depend on the nature of the drug or treatment; for a drug which seeks to minimize the damage produced by a vascular occlusion, either by augmenting blood flow or increasing the at risk brain tissue’s resistance to ischemia, it would be important to know the nature and severity of the offending vascular lesion, the severity of the deficit, and the state of the ischemic brain. For therapies that are aimed prophylactically at preventing the next stroke, the nature of the vascular lesion would seem to be the most important variable and the severity of the present deficit of lesser import.

Concepts are difficult to visualize in the abstract so perhaps a few examples will help clarify these strategies. In studying therapies which purport to modify the outcome of the acute stroke such as Fluosol-DA, pentoxiphyllin, prostacyclin, naloxone, or hemodilution, one could choose groups matched for their occlusive lesion (e.g. severe stenosis or occlusion of the internal carotid artery or middle cerebral artery), severity of clinical deficit, and presence and size of CT scan lesion. Severity of clinical deficit would need to be quantitated using a stroke severity score which considered clinical signs such as the degree of hemiplegia as well as measures of functional capabilities in activities of daily living (ADL) tasks such as the Barthel’s index. Inclusive limits can be placed on each of these variables e.g. residual vascular lumen 0–1 mm, severity score of 30–50 units, CT positive for lesion ½ to 1 cerebral lobe in size. If there is interest in other variables such as blood flow and metabolism data from Xe flow, SPECT or PET could be used; the groups could then also be subsequently analyzed for these factors. Patients fulfilling all 3 necessary criteria could be placed into placebo or therapeutic groups and the results analyzed. Alternatively one could choose one critical variable such as presence of an angiographically documented occlusive lesion and place patients into different treatment groups. Later analysis could study the effects of stroke severity, CT positivity etc. The last example might prove particularly applicable to studies of prophylactic stroke prevention. The questions to be answered are innumerable. Do patients with nonstenosing carotid plaques and less than complete infarction in the ipsilateral middle cerebral artery territory do better with antiplatelet agglutinating agents, warfarin or prophylactic surgery? Do patients with total internal carotid artery neck occlusions and slight to moderate deficits do better prophylactically with superficial temporal artery to middle cerebral artery shunts and do blood flow or CT findings predict prognosis? Do patients with small middle cerebral artery superficial infarcts and normal noninvasive cardiac and carotid tests and normal blood do better with anti-platelet agents or warfarin?

Admittedly large numbers of patients and cooperation between centers will be required to obtain results which are important and statistically and clinically valid. Despite the difficulties of such trials, we have reached a point in our technical sophistication when they are plausible and needed. We cannot continue the old bankrupt strategy of grouping patients only by temporal description of their symptoms, an idea which has an unsatisfactory past and no future.

Hopefully we are entering a new era in stroke treatment based on advancing technology and careful study of groups of patients. We must begin to shed the older methods of studying large heterogenous groups of patients sharing only a chronological characterization such as TIA, RIND, completed stroke etc. Like Hans Brinker with his finger in the dike, these studies were useful when that’s all we had. We now have bought the clinician new clothes; let’s hope they will turn out to be substantial and will allow him to discard his former rags without too many shed tears.

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