Tissue Viability Thresholds in Acute Stroke
The 4-Factor Model

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And the LORD said, “Behold, they are one people, and they have all one language; and this is only the beginning of what they will do; and nothing that they propose to do will now be impossible for them.”

Genesis 11:6

Defining thresholds of tissue viability in ischemic stroke is not quite a problem of biblical proportions, but it has become a matter reminiscent of the story of Babel. From the earliest PET studies of altered tissue hemodynamics and metabolism 2 decades ago through the most sophisticated multiparametric models using MRI, investigators have worked to determine thresholds on imaging measures of stroke patients that would distinguish regions destined to recover spontaneously, from those irreversibly injured and destined to infarct, from those threatened but potentially viable—the ischemic penumbra. The answer has been given dozens of times by dozens of investigators, and it has been a different answer each time it has been given. This observation is not meant to be dismissive of the important work that has been done toward this goal, but to underscore the difficulty in studying the problem, a difficulty compounded by the fact that no two investigative groups have approached the problem in the exact same manner.

The articles of Oppenheim and colleagues in the current and recent issues of Stroke are excellent examples of MRI work investigating the value of single tissue parameters in predicting outcome. Their studies contained relatively large sample sizes for studies of this type. The patients were untreated and studied within 6 hours of symptom onset, the type of patients of greatest interest for a model to discriminate salvageable from unsalvageable tissue. Although single tissue parameters such as the apparent diffusion coefficient (ADC) are predictive of tissue outcome, a single parameter cannot give an absolute threshold. The evolution of ischemic injury is a dynamic process at best, approximated from a single parameter at a single imaging time point. The ADC value reflects only the ischemic history of the tissue, whereas hemodynamic parameters are indicative of the ischemic future of the tissue. In the sample reported by Oppenheim and colleagues, the relative hemodynamic changes were also predictive of tissue outcome, but no statistical comparison was reported among the ADC and perfusion parameters for their relative potential to distinguish viable tissue. Further studies will be needed to determine whether these ADC thresholds are similarly predictive in the stroke population at large. A combination of perfusion and diffusion parameters into statistical models would be expected to add even more predictive power. Recent work has shown that ADC, as commonly measured, is contaminated by cerebrospinal fluid and that true parenchymal ADC measurement in ischemic tissue may be approximately 15% lower in the earliest hours after onset. Current models of ADC thresholds may need to be revised using purer measures of parenchymal ADC.

Four major factors interact to determine tissue outcome. Any one factor may be predictive, but multiple factors will provide more predictive power. The complete model of tissue viability must contain these factors: a time factor, a hemodynamic factor, a tissue factor, and an intervention factor. There is no absolute viability threshold that is independent of time, but there is also no absolute time window of tissue viability. Time from onset reflects the duration of hemodynamic changes, although in clinical practice reported onset time of ischemic symptoms may not always correspond to onset of ischemia. Ischemia must be of sufficient duration and severity to lead to infarction. Time is an implicit factor in the analysis of Oppenheim and colleagues, as their results apply specifically to the time from onset in their sample and would likely be different in a sample studied 6 to 12 hours from onset. Early pathological ADC changes are reversible with reperfusion or pharmacological intervention, so any threshold of ADC will depend on the values of the other factors. Measurement of patients at multiple time points within the acute period will add predictive power, as it will more accurately reflect the dynamic nature of ischemic changes and their effects on tissue. Ischemic stroke is by definition a disease of altered cerebral hemodynamics, and a model that does not include a direct measure of hemodynamics will be lacking. Altered hemodynamics may be measured across the breadth of neuroimaging modalities as quantitative or qualitative indices of cerebral blood flow, blood volume, or mean transit time. Tissue factors may include local metabolic, genetic, hemostatic, vascular, or structural changes secondary to ischemia or may be preexisting determinants of susceptibility to ischemic injury. Parameters of ADC and T2 are commonly used as tissue factors in MRI-based models. Clinical features associated with outcome, such as age,
gender, serum glucose, temperature, and blood pressure, will modify the effects of hemodynamic and tissue factors.

Tissue viability predictions will depend on the presence and timing of a therapeutic intervention, a factor just emerging into models. Reperfusion or cytoprotection by endogenous, pharmacological, or mechanical mechanisms will have their own unique viability signatures, which may overlap but are unlikely to be identical.

The range of measurable hemodynamic and tissue factors is broad and will likely broaden with further advances in imaging and other tissue-monitoring techniques. Inclusion of multiple levels of any of these factors may add incrementally to the predictive power of a model, but the most explanatory power will come with incorporation of each of these 4 major factors.

How the imaging measurements are made and analyzed has received little attention. Study-to-study variability in sample characteristics, patient management, image acquisition techniques, image processing methods, image parameter segmentation, and statistical models will affect the specific models and thresholds that are reported. Inconsistency in the approach to this problem threatens to increase the noise in the literature to a level that may impede progress. How useful are predictive models of tissue outcome if no two groups of investigators use the same approach and no one approach has been proved to be superior to another? Can we hope to discover and validate a method that will predict tissue and patient outcome and distinguish responders from nonresponders and high-risk from low-risk patients if we cannot agree on how to measure and model these outcomes?

The solution is to compare the different predictive models on large sample sets of the same patients, thereby controlling for differences in acquisition, ischemic dynamics, clinical features, final infarct, and other individual differences. If no significant difference among predictive models can be found, the simplest model will be preferred. The model with the fewest steps in image processing required will be preferred, because every data transformation invariably results in loss of information, and it will also be the one easiest to apply to clinical practice. For MRI of acute stroke, until a more accurate and more sophisticated model is validated and accepted, the simple model of the diffusion-perfusion mismatch as the predictor of tissue outcome will continue to dominate the field because of its ease of use and unequivocal relationship to infarct growth.

Such a comparison would take an unprecedented degree of data pooling and collaboration among research groups but may be the only way to advance the field beyond the current proliferation of models, signatures, and thresholds, each of which is unlikely to be used except by the investigator involved in its generation. Because our “Tower of Babel” problem has not been the result of divine intervention meant to confuse and prevent us from reaching our goal but is one of our own creation, the solution is also within our power.

References

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