Controversies in Stroke

Section Editors: Geoffrey A. Donnan, MD, FRACP, and
Stephen M. Davis, MD, FRACP

Measurement of the Ischemic Penumbra With MRI:
It’s About Time

Steven Warach, MD, PhD

The idea that there exist 2 ischemic thresholds in the pathogenesis of cerebral infarction came from seminal microelectrode studies of the baboon cortex the late 1970s that measured the effects of progressive reductions in cerebral blood flow (CBF). These studies described a level of CBF reduction that led to cessation of cortical evoked responses in the absence of terminal increases in extracellular potassium or reductions in pH and a yet lower level of CBF reduction, at which occurred large increases in extracellular potassium and reductions in pH indicative of failure of membrane ion homeostasis and cell death.

Derived from animals too few and results too variable to specify a precise threshold, the insight nonetheless emerged that there were 2 levels of ischemia, one for tissue dysfunction without destruction and a lower one for irreversible cell injury. The metaphor of the ischemic penumbra was coined to describe this intermediate zone of ischemia between functionally normal and dead brain tissue. Restoration of normal CBF to the penumbral zone may reverse the functional disturbance.

Over the past 25 years, many investigators and clinicians have taken poetic liberties with the ischemic penumbra to suit their technologies and purposes. To some it is any variable that is intermediate in value between normal and that measured within the infarct. To others it is simply any noninfarcted brain with reduced CBF. To still others it is that region that is the optimal target of stroke therapy, destined for infarction if untreated but potentially salvageable if effectively treated. This last interpretation is of greatest relevance for the stroke patient and for the development of stroke therapies.

To the originators of the concept, the penumbra was defined by the tip of a microelectrode. Neither multitracer PET nor diffusion-perfusion MRI nor any noninvasive neuroimaging technique can accurately measure the penumbra by the original definition. None have determined reliable, validated absolute thresholds for the upper and lower CBF boundaries of the penumbral zone, and none will. As we have argued elsewhere, the very notion of a specifiable absolute CBF threshold of tissue viability is meaningless if it is not integrated with temporal, therapeutic, and tissue factors. Definitions of penumbra that do not account for the time course of the physiological perturbation and the effects of physiological or pharmacological manipulations will be of limited value. The quantitative precision and range of metabolic variables measurable by PET should, in principle, make it the method of choice for imaging the human penumbra.

However, limited numbers of PET centers exist and even fewer that can routinely study patients within the critical first few hours after a stroke. This fact and other practical limitations related to availability, radiation exposure, and arterial catheterization constrain the use of PET as a tool for managing acute stroke patients and assessing investigational therapies.

By contrast, diffusion and perfusion MRI of the less-than-6-hour stroke patient are routinely performed in hundreds of centers and have been a key element in several multicenter acute stroke trials. The goal in measuring the penumbra is to identify the patient with salvageable tissue-at-risk that is amenable to therapy. This requires a methodology that can be used emergently and used in large-scale randomized controlled trials to select patients and evaluate interventions. From the initial observations of whole brain diffusion and perfusion MRI in hyperacute stroke patients, it was evident that a larger region of hemodynamic compromise on PWI was present than the region of reduced apparent diffusion coefficient (ADC) induced by critically low CBF. The ADC on DWI reflects the CBF history of the tissue and evolves into infarction without reperfusion or neuroprotection. Hemodynamic abnormalities on PWI predict the possible futures of lesion evolution, futures affected by reperfusion and other potentially therapeutic interventions. This mismatch region is the tissue-at-risk and related to worse clinical outcome and infarct growth if early reperfusion does not occur.

The importance of this mismatch in predicting lesion expansion and growth has been described in many series from many different centers, and prospectively confirmed in a multicenter clinical trial. Quantitative models of multiparametric
MRI markers of the penumbra have been developed and may lead to improvements in MRI patient selection beyond qualitative diffusion-perfusion mismatch assessments. Considerable data have emerged suggesting that the selection of patients by the diffusion-perfusion mismatch may identify the appropriate patient for effective intravenous thrombolytic therapy beyond 3 hours from onset,9–11 and several randomized, placebo-controlled, multicenter trials are in progress to test that hypothesis.

The superior quantification by PET is indisputable but, paradoxically, not relevant to this discussion. What is the better measure of the ischemic penumbra in human stroke? The better technique is the one that will lead to effective stroke therapies. MRI is more likely than PET to achieve that goal.

References

Best Measure of Ischemic Penumbra: Positron Emission Tomography

W.-D. Heiss, MD

The ischemic penumbra was defined by Astrup et al1 as brain tissue perfused at a level within the thresholds of functional impairment and morphological integrity, which has the capacity to recover if perfusion is improved. Because tolerance of tissue to ischemic damage is dependent on residual flow and duration of flow disturbance,2 the ischemic penumbra characterizes a transient condition: it exists for a short period even in the center of ischemia, and may extend to increasing time periods in the more or less hypoperfused surrounding tissue. The concept of the ischemic penumbra has been developed from animal experiments in which regional flow measurements could be clearly related to the functional/morphological state of the tissue. Its transfer to the clinical situation requires the definition of 3 critical values that usually cannot be assessed in the acute stage of ischemic stroke: (1) quantitation of flow in the core and the periphery of the territory with impaired blood supply; (2) state of the various tissue compartments within the affected area with respect to irreversibly damaged or preserved morphology; and (3) the time period the respective tissue compartments have been exposed to more or less hypoperfusion. As all clinically available methods at best yield only momentary assessments of brain perfusion and tissue condition at several hours after the vascular attack, the development of these changes over time remains obscure, and predictions on the fate of the tissue from the measurable variables must be vague. Therefore, the definition of penumbra tissue in the clinical setting is limited to accurate assessments of perfusion in the core, the periphery and the surrounding of the territory with impaired blood supply, and the detection of irreversibly damaged tissue at the time of investigation.

Positron emission tomography (PET) was leading in the clinical assessment of the penumbra: multitracer studies defined the penumbra as tissue with reduced cerebral blood flow (CBF) but preserved oxygen consumption (CMRO2) and raised oxygen extraction fraction (OEF).3,4 For the

References
definition of irreversible tissue damage at the time of investigation (usually several hours after the ischemic event), the cerebral metabolic rate for oxygen (CMRO₂) is the most reliable parameter with \( \sim 65 \ \mu\text{mol} \cdot 100 \ \text{g}^{-1} \cdot \text{min}^{-1} \) as the threshold. In the studies relating early CBF and CMRO₂ measurements to infarcts determined on late CT, a flow threshold of 12 mL \( \cdot 100 \ \text{g}^{-1} \cdot \text{min}^{-1} \) was described, which also predicted irreversible damage. These determinations of flow and energy metabolism, however, require complex logistics for investigations of acute stroke patients and necessitate arterial blood sampling, and therefore are difficult to perform in the clinical setting and prohibited when invasive therapies, eg, thrombolysis, are planned. Therefore, tracers are required that indicate tissue integrity or hypoxia, and in combination with semiquantitative determinations of perfusion can outline noninvasively the extent of penumbra tissue. The central benzodiazepine receptor ligand flumazenil (FMZ) labeled with 11-C is a marker of integrity and detects neuronal damage in the cortex in the first hours after ischemic stroke. The extent of decreased accumulations of this tracer in the cortex correlates significantly with the extent of tissue with CMRO₂ reduced below the critical threshold and identifies irreversible damage even in areas with increased OEF. Tissue compartments with FMZ binding below a critical threshold cannot benefit from reperfusion—a finding that also supports the ability of the tracer to identify developing infarcts.

In a study in which the final infarcts were analyzed with respect to flow values and FMZ uptake in the first hours after stroke, probability thresholds of FMZ binding and blood flow could be calculated, which predicted the final state of the tissue and defined the range of the penumbra. As the 95% prediction limit for infarction the FMZ uptake was detected 6.25 to 42.5 hours after stroke. It is maximal in the initial hours after onset, declines with time, and is absent after several days. The areas were usually distributed over the periphery of the infarct identified on the coregistered late CT, but extended into normal tissue adjacent to the infarct in a few cases. These findings suggest that FMISO binding is increased in tissue at risk and mirrors the temporal and spatial distribution of penumbra. However, these results need direct calibration by conventional PET measurements. Since reliable detection of FMISO uptake is delayed (>2 hours between tracer injection and imaging), the value of this tracer is limited for therapeutic decisions in the acute phase of ischemic stroke.

As long as other imaging modalities do not yield reliable detection of irreversible tissue damage—even diffusion-weighted MRI might be misleading in some cases—and do not furnish quantitative values of blood flow for the upper limit of penumbra, PET procedures must be considered still the gold standard for the recognition of penumbra. However, PET is limited by the required expensive equipment and the complex logistics involving a multidisciplinary team. Therefore, time has come to calibrate simpler and widely applicable functional imaging procedures—especially diffusion- and perfusion-weighted MRI—on PET in order to make these modalities a reliable tool in the study of acute ischemic stroke.

References

KEY WORDS: cerebral blood flow | tomography, emission computed | penumbra | stroke, ischemic
"...the outcome of incomplete cerebral ischemia is of particular interest...one hopes it will become possible to conduct treatment and to evaluate prognosis in the acute stroke patient by reproducible repeatable measurement in man."

Astrup et al

Why is the penumbra so important? In the 1970s it gave us the first insight into the prolonged nature of tissue survival after stroke. In the 1990s its importance as a target for therapy was confirmed with the introduction of tPA as the first treatment aimed at rapid reperfusion and salvage of critically hypoperfused brain.

The protagonists have nicely positioned the current status of in vivo measurement of the penumbra. On one hand we have PET, which has provided such important biological insights (particularly quantitative) into penumbral characteristics such as blood flow and metabolism, while on the other we have the pragmatic advantages of MRI. PET and MRI provide complementary information about a phenomenon that can be defined in more than one way. Both techniques have contributed enormously to our current understanding of tissue viability.

We are, therefore, of the view that there is no gold standard for human penumbral measurement. Indeed, both PET and MRI concepts continue to evolve. For example, as outlined by Heiss, we have moved from the original $^{15}$O techniques through to $^{11}$C flumazenil and $^{18}$FMISO. Using MRI, the mismatch concept (hypoperfusion volume > DWI lesion core) has been modified with the recognition that a portion of hypoperfused brain reflects benign oligemia and that the DWI core may be partially salvageable. Other incremental refinements, including measurement of biochemical thresholds with spectroscopy, are likely to occur. Even imaging of a "molecular penumbra,” with measurement of gene markers of protein expression, cannot be discounted.2

Measurement of the penumbra is being utilized in proof of concept stroke trials. Further, patient selection based on penumbral presence in clinical trials is being explored. Hence, the introduction of new therapies is likely to catalyze improvements in penumbral imaging and measurement, even more quickly than before.

References

Key Words: magnetic resonance imaging • penumbra • therapy • tomography, emission computed
Ischemic Penumbra: MRI or PET
Stephen M. Davis and Geoffrey A. Donnan

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