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

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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

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Best Measure of Ischemic Penumbra: Positron Emission Tomography

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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 severe 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
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 \( \approx 65 \mu \text{mol} \cdot 100 \text{g}^{-1} \cdot \text{min}^{-1} \) 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.⁴

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.⁵ As the 95% prediction limit for infarction the FMZ uptake was 3.4 times the average of white matter was found, as the flow range for the penumbra 4.8 to 14.1 \( \mu \text{mol} \cdot 100 \text{g}^{-1} \cdot \text{min}^{-1} \) were obtained.

Due to the low concentration of benzodiazepine receptors in white matter and basal ganglia, these values apply only to the cortex but still permit a reliable measure of irreversibly damaged and potentially salvageable portions of an ischemically compromised area. These values are comparable to those determined in invasive studies if the errors inherent in determinations based on low count rates are taken into consideration.

As a tracer of hypoxic viable tissue, 18-F-fluoromisonidazole (FMISO) could also be used to detect ischemic penumbra. Areas with increased FMISO uptake were 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.⁶ 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—one 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
Ischemic Penumbra: MRI or PET

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"... 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 15O techniques through to 11C flumazenil and 18FMISO. 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.

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
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